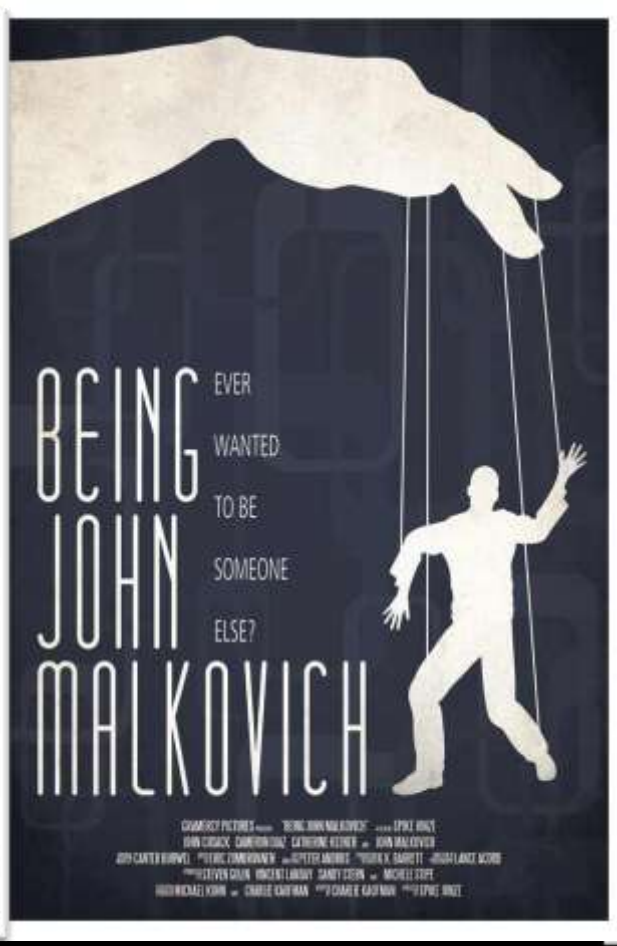
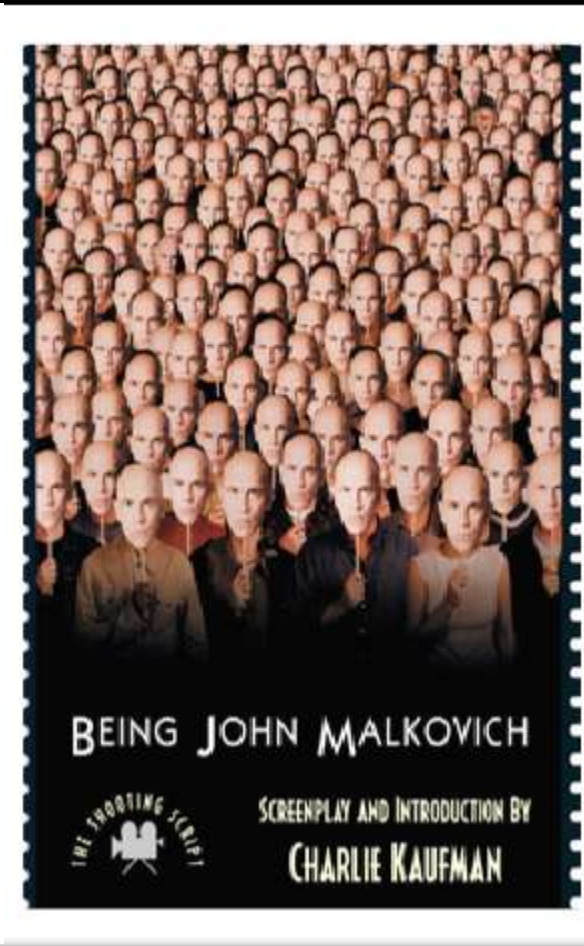
Acute Kidney Injury (AKI):

beyond “RIFLE” and “AKIN”

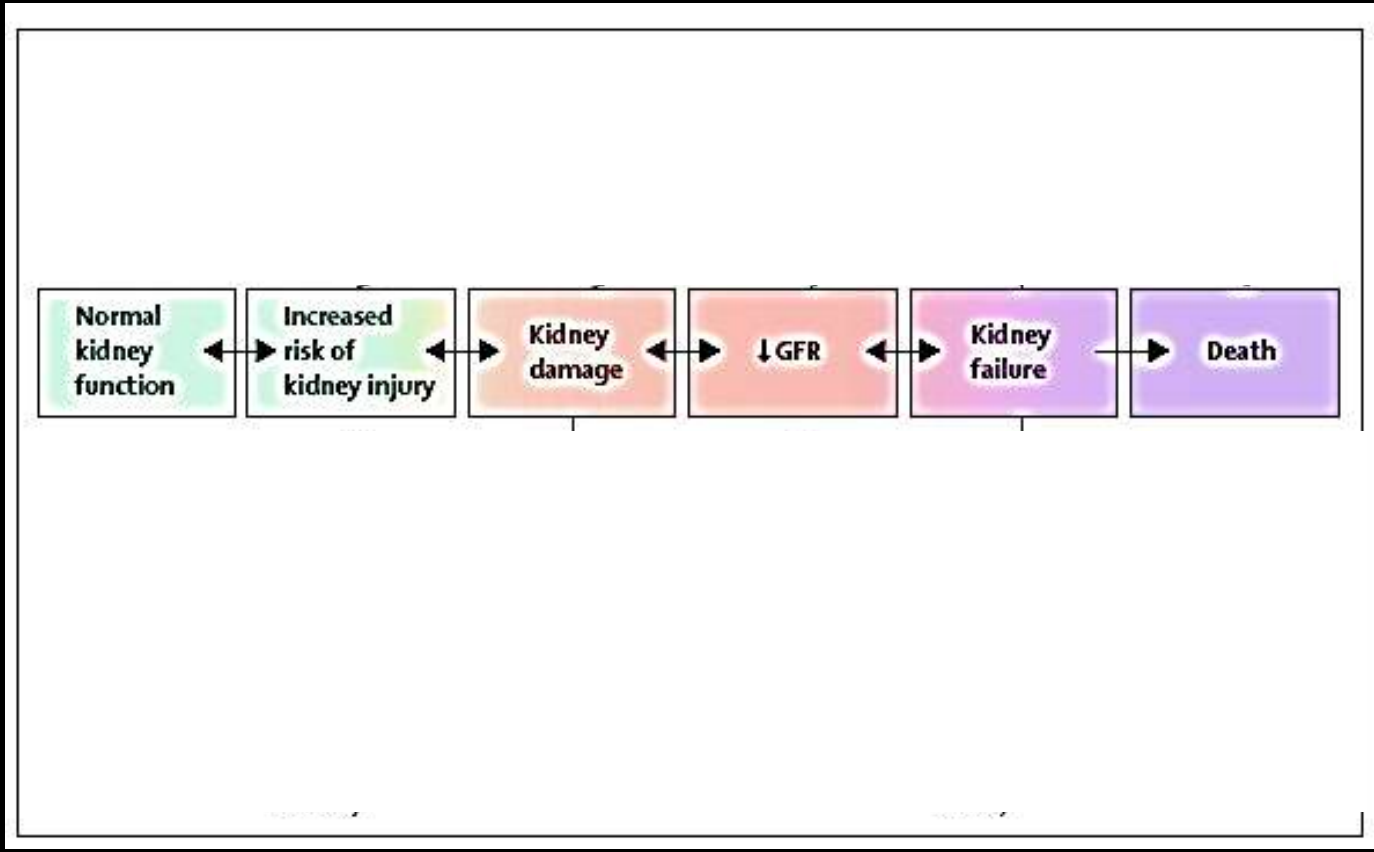
Saddam Hassan
MD
Benha University
February 2015


BEING JOHN MALKOVICH
EVER WANTED TO BE SOMEONE ELSE?


BEING JOHN MALKOVICH
THE SHOOTING SCRIPT
SCREENPLAY AND INTRODUCTION BY
CHARLIE KAUFMAN

AKI:

Rinaldo Bellomo, John Kellum, Claudio Ronco Lancet (2012)



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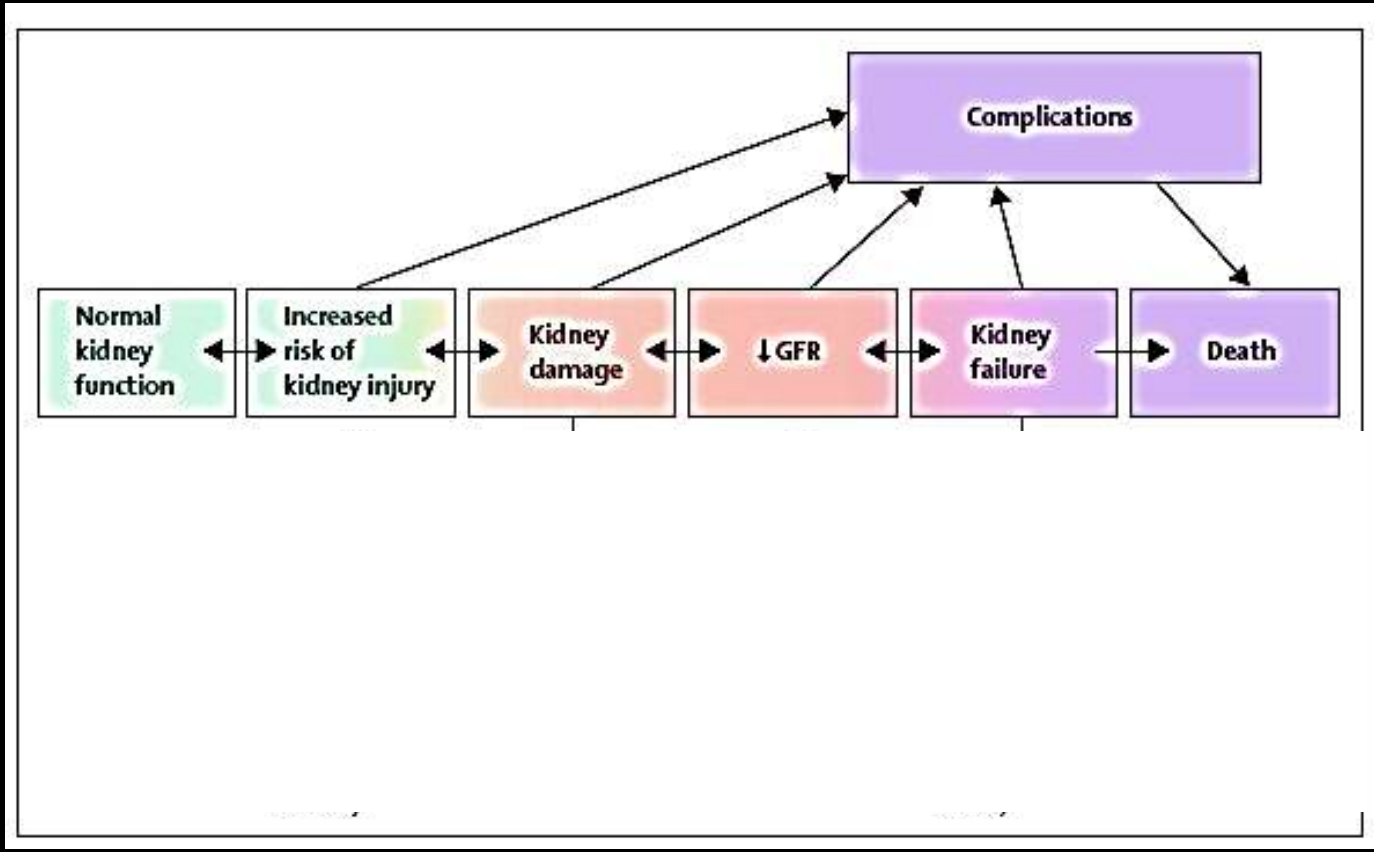
Rinaldo Bellomo, John Kellum, Claudio Ronco Lancet (2012)



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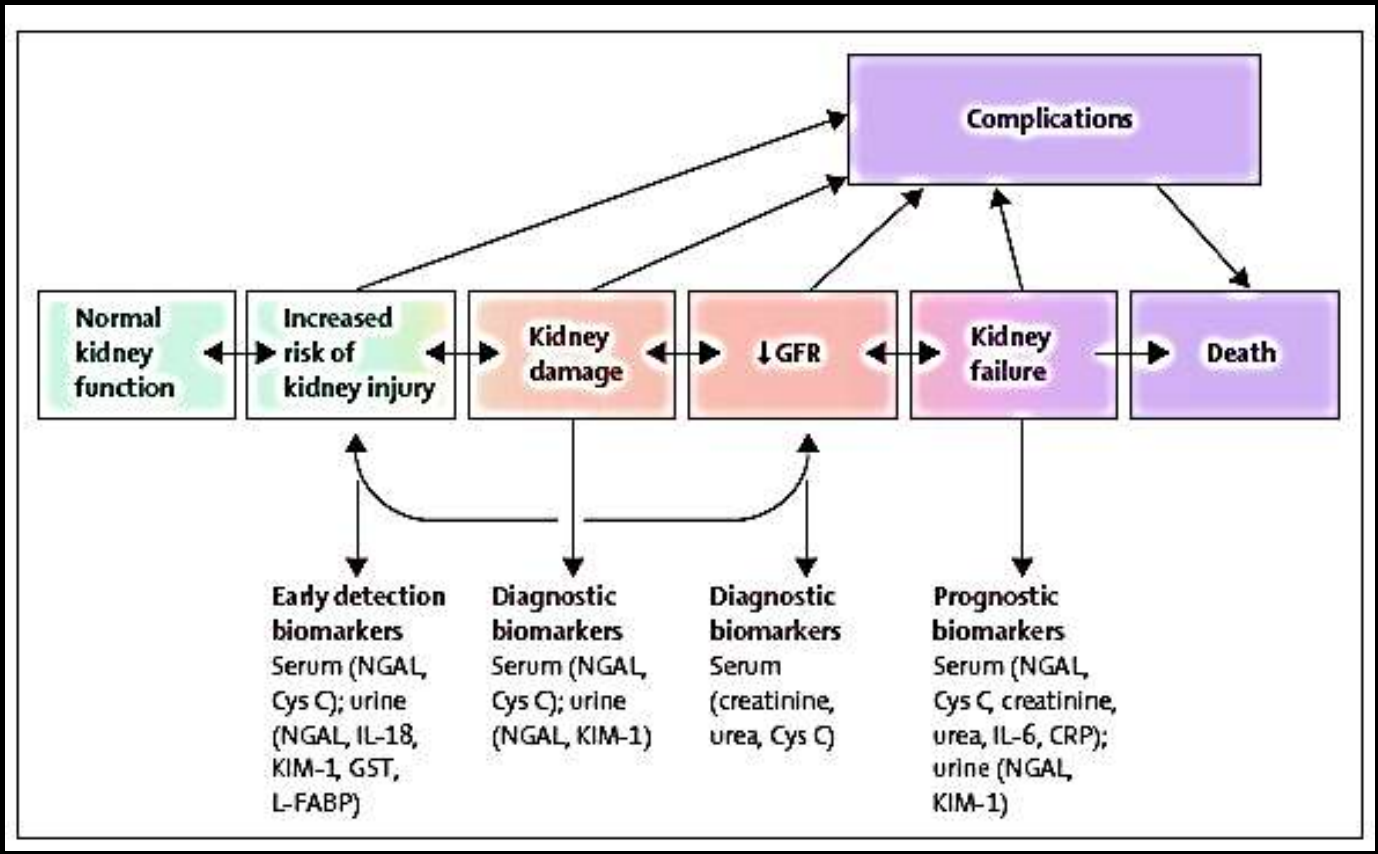
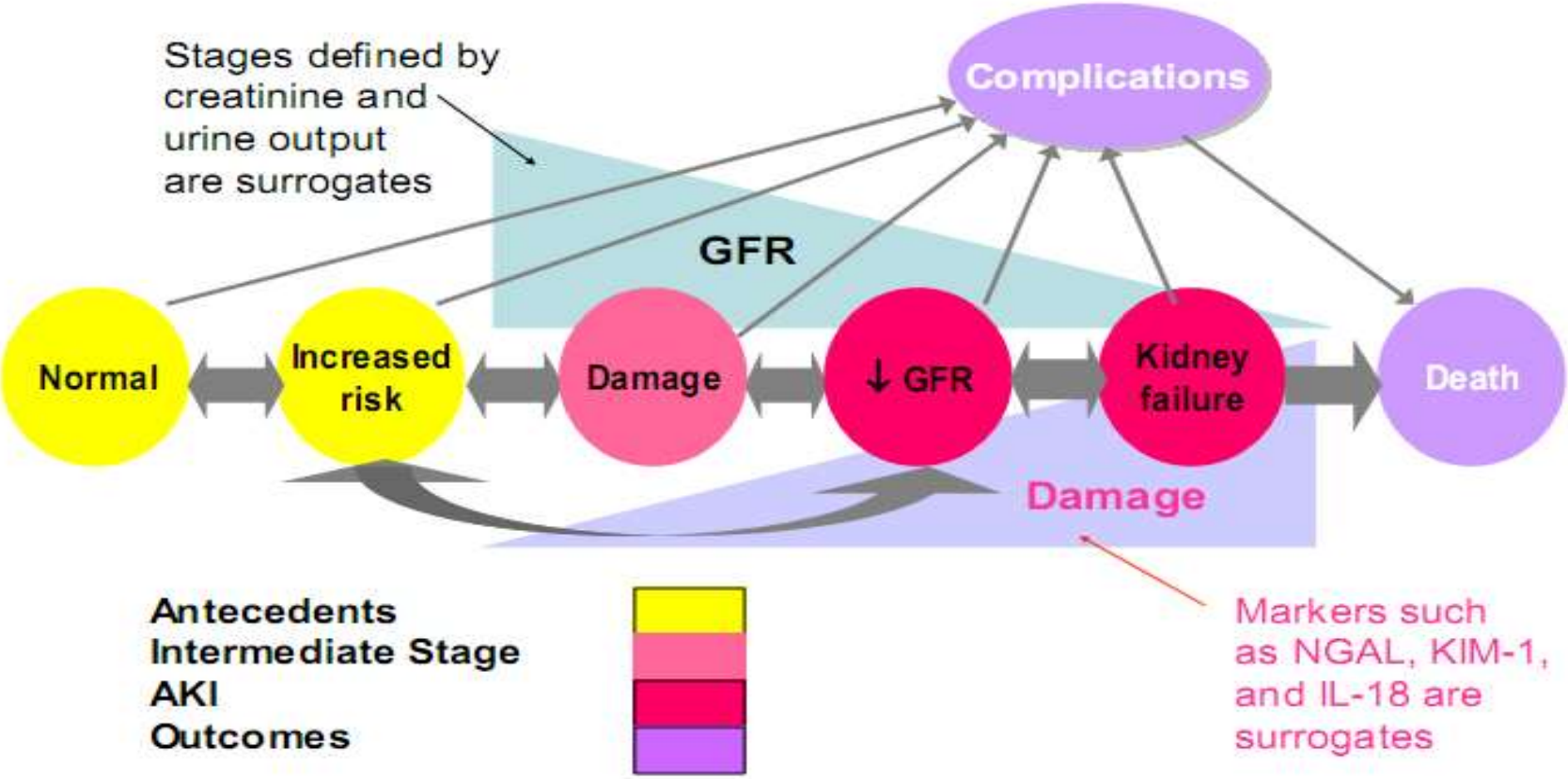


AKI: KDIGO 2012

Kidney International Supplements

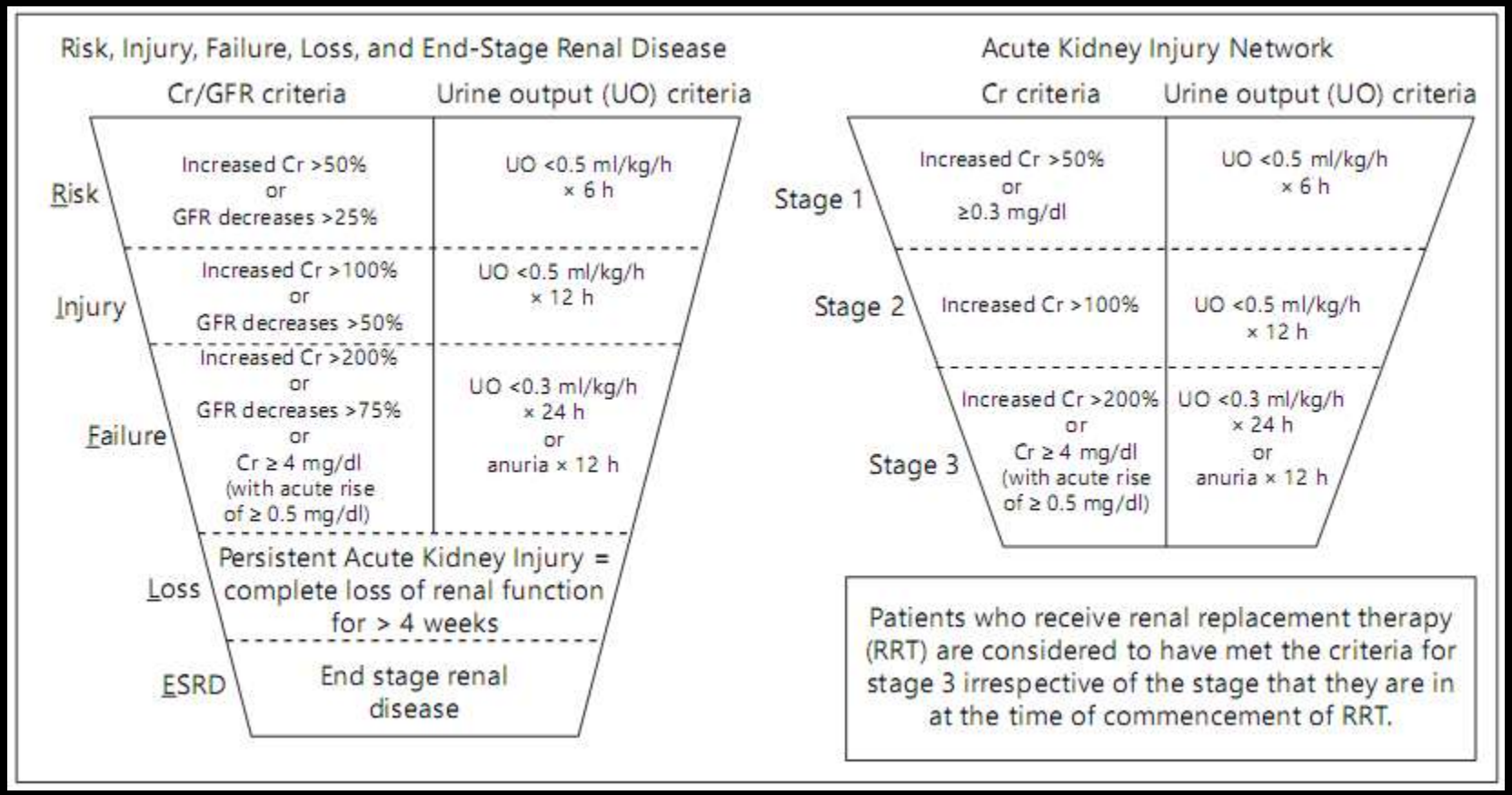


Clin Kidney J (2013) 6: 8–14
doi: 10.1093/ckj/sfs160

CKJ

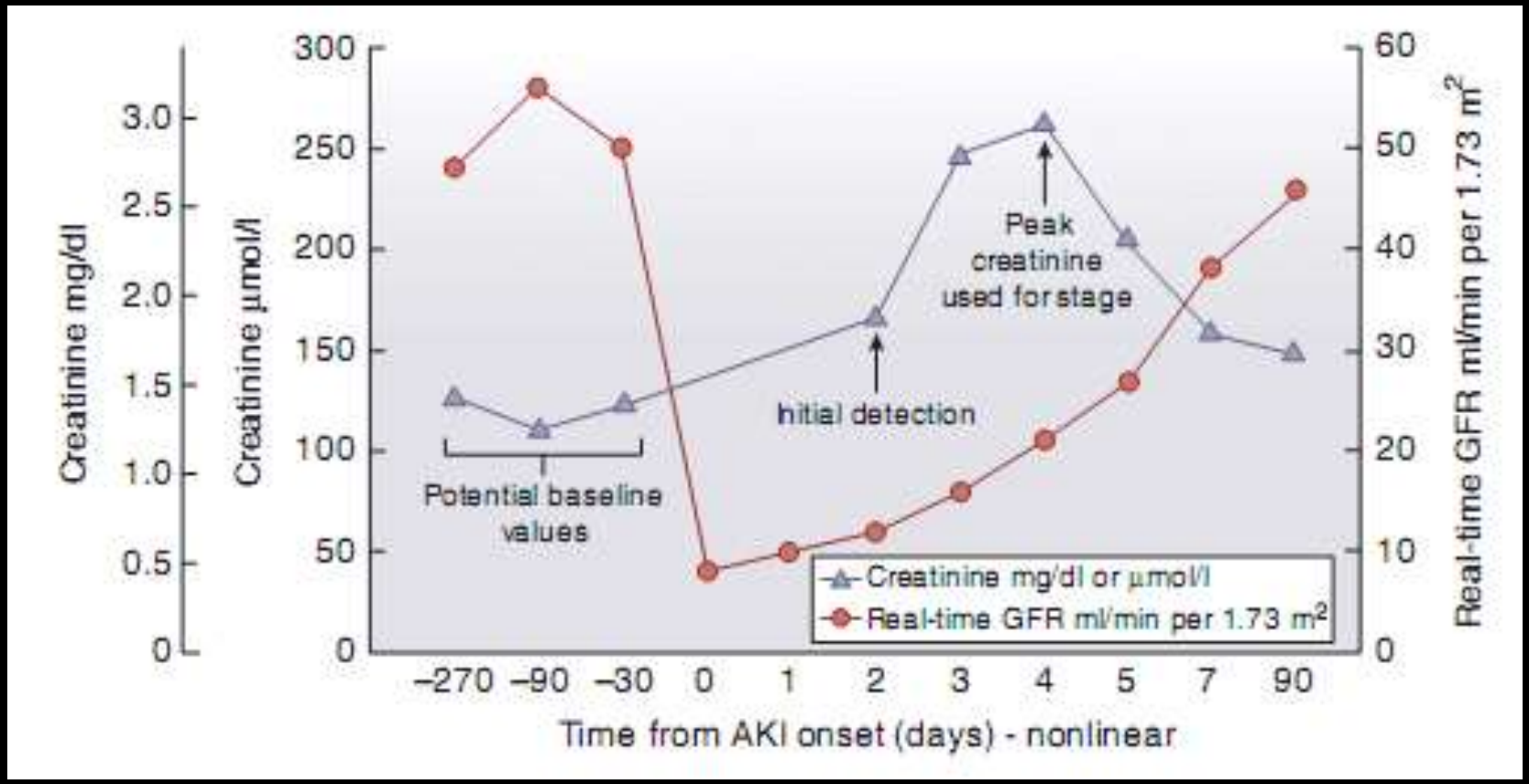
In Depth Review

The RIFLE and AKIN classifications for acute kidney injury: a critical and comprehensive review



“ The Gold Standard “sCR.” !!

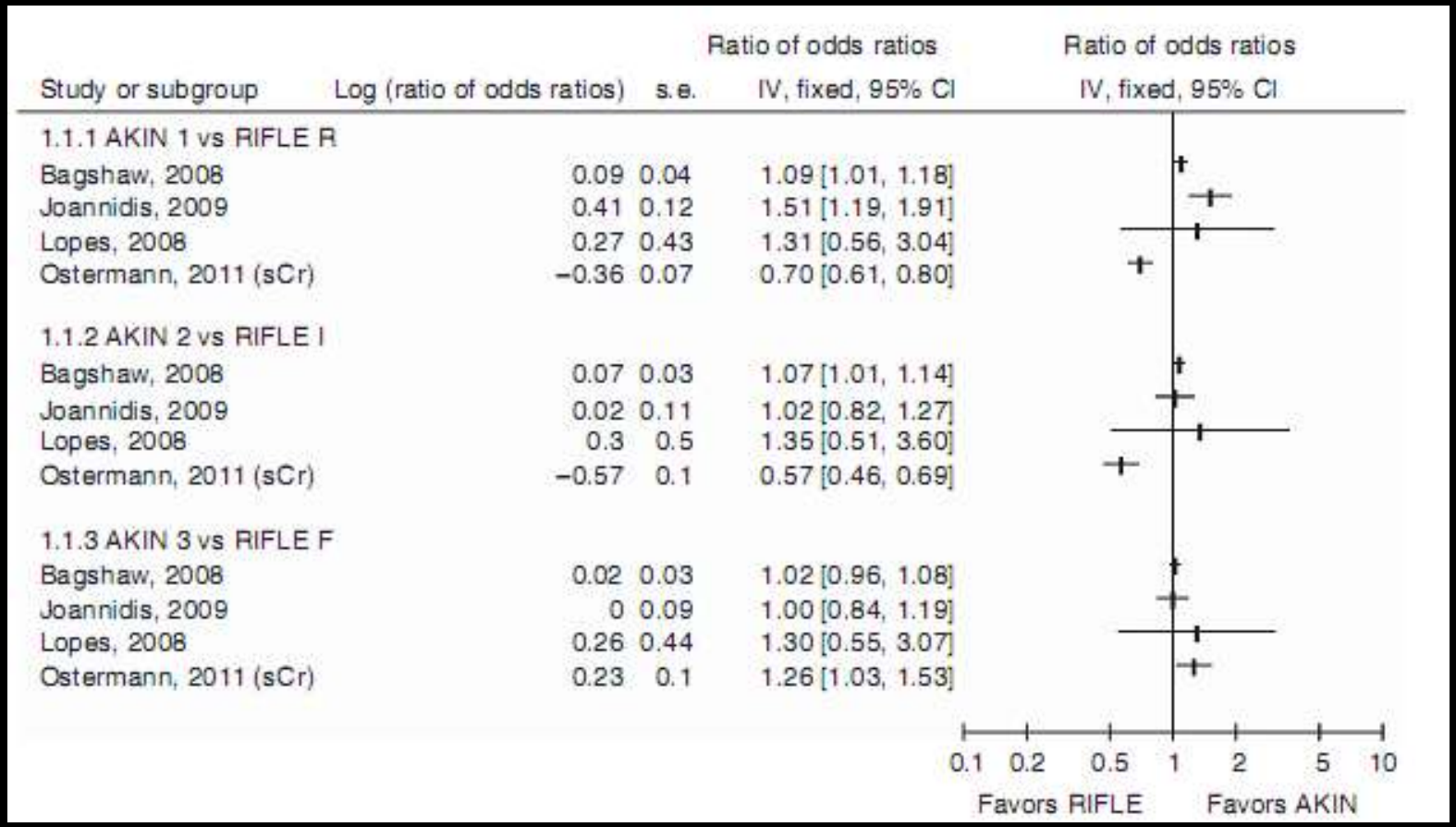
Thomas et al.: “The definition of AKI” KI 2015



Mortality: Validation metric

Thomas et al.: “The definition of AKI”

KI 2015



KDIGO 2012

Ungraded

NDT
Nephrology Dialysis Transplantation

ERBP 2012

Stage	Serum creatinine	Urine output
1	1.5–1.9 times baseline OR ⩾0.3 mg/dl (⩾26.5 μmol/l) increase	<0.5 ml/kg/h for 6–12 hours
2	2.0–2.9 times baseline	<0.5 ml/kg/h for ⩾12 hours
3	3.0 times baseline OR Increase in serum creatinine to ⩾4.0 mg/dl (⩾353.6 μmol/l) OR Initiation of renal replacement therapy OR, In patients <18 years, decrease in eGFR to <35 ml/min per 1.73 m^2	<0.3 ml/kg/h for ⩾24 hours OR Anuria for ⩾12 hours

Stage 1: one of the following:
- Serum creatinine increased 1.5–1.9 times baseline
- Serum creatinine increase >0.3mg/dl (26.5 μmol/l)
- Urinary ouotput < 0.5ml/kg/h during a 6 hour block

Stage 2: one of the following
- Serum creatinine increase 2.0–2.9 times baseline
- Urinary output <0.5ml/kg/h during two 6 hour blocks

Stage 3: one of the following:
- Serum creatinine increase >3 times baseline
- Serum creatinine increases to >4.0mg/dl (353 μmol/l)
- Initiation of renal replacement therapy
- Urinary output <0.3ml/kg/h during more than 24 hours
- Anuria for more than 12 hours

The Simply Referred to as " Baseline sCR."

Thomas et al.: "The definition of AKI" KI 2015

Methods of baseline determination	Comments
Use of creatinine results within last 7 days	• May need high rate of imputation—in one study, 29% of patients had a creatinine within 7 days of admission[81] • Risk of creatinine elevated by prodrome being used as 'baseline'—hence, extent of AKI underestimated[81]
Admission creatinine	• Higher than outpatient creatinine; reduced detection of AKI—likely reflects community-acquired AKI[83]
Minimum inpatient value during first 7 days of admission as baseline	• KDIGO suggested the use of lowest creatinine during hospitalization[3] • Lower than outpatient creatinine • Overestimates prevalence of AKI[83]
Imputation or back-calculation by reversing MDRD equation using age, sex, and an assumed normal GFR of 75 ml/min per 1.73 m^2	• Baseline creatinine will often be underestimated, and GFR overestimated, notably in CKD[84] • Prone to error[83,85,86]
Mean outpatient value as baseline (−7 to −365 days look-back[a])	• Highest correlation 0.91[b] with adjudicated baseline value—availability 81% of patients in the study[81]
Most recent outpatient value as baseline (−7 to −365 days look-back[a])	• Moderately lower correlation 0.84[b] with adjudicated baseline value[81]
Lowest or nadir outpatient value as baseline (−7 to −365 days look-back[a])	• Moderately lower correlation 0.83[b] with adjudicated baseline value[81]
Most recent inpatient or outpatient value as baseline (−7 to −365 days look-back[a])	• Allows inclusion of last creatinine from previous inpatient stay if ⩾7 days away • May allow simpler programming • Correlation 0.88[b] with adjudicated baseline value—availability 93% of patients in study[81]
Extended baseline look-back (−7 to −730 days)	• Improved availability of baseline creatinines but some drop in correlation with adjudicated baseline[81]
Multiple imputation	• Recently assessed as a research technique[87]

How Can We Define Recovery after AKI?

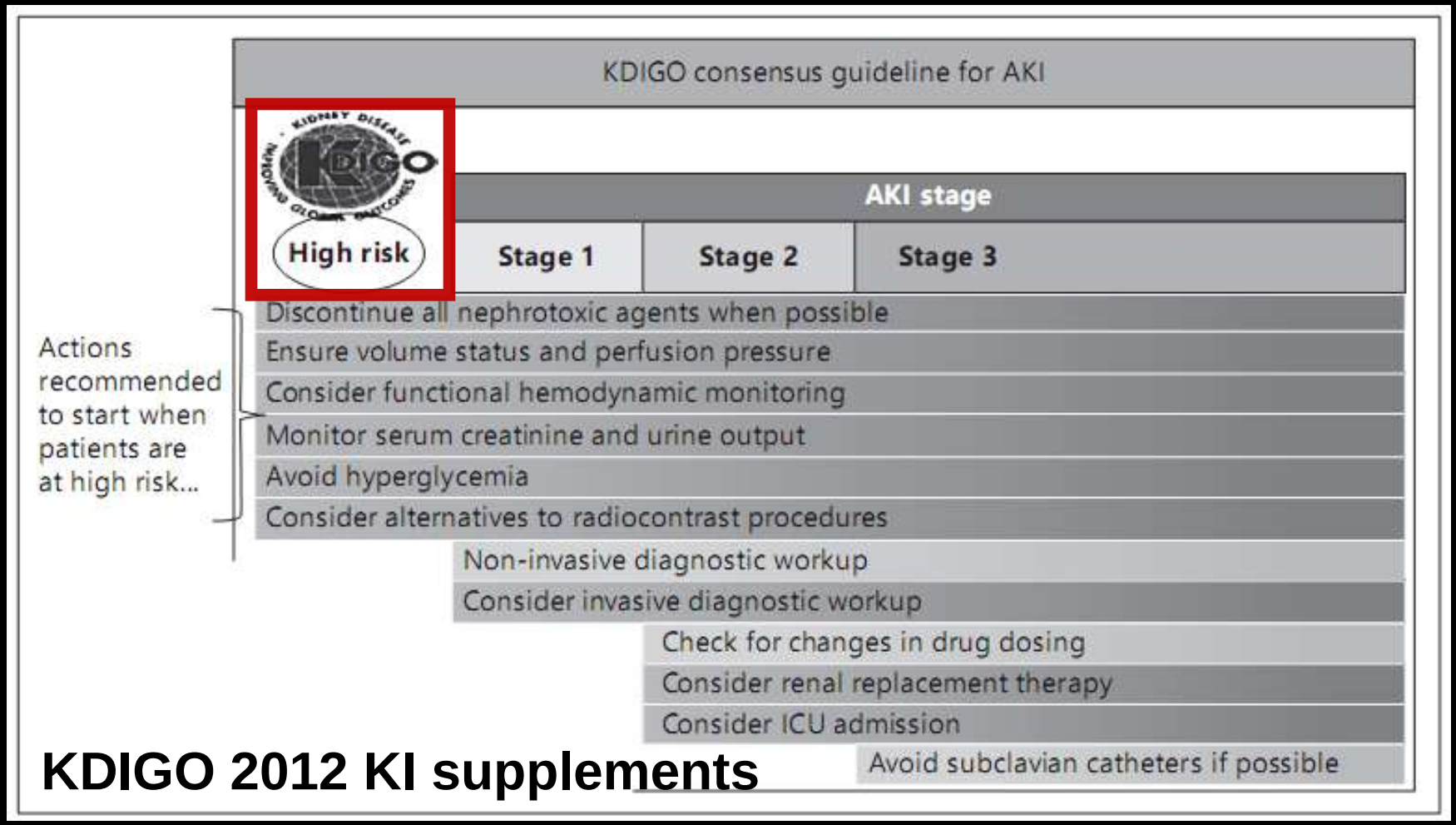
John A. Kellum Nephron Clin Pract 2014

	ADQI [1] 2004	ATN Trial [25] 2008	Srisawat et al. [19] 2011	KDIGO [3] 2012
Complete recovery	Return to within 50% of baseline serum creatinine	Return to within 0.5 mg/dl of baseline creatinine	Alive, no RRT, less than RIFLE-F criteria	GFR ≥60 ml/min/1.73 m^2
Partial recovery	Off RRT but failed to return to within 50% of baseline serum creatinine	Off RRT[a] but failed to return to within 0.5 mg/dl of baseline creatinine		Off RRT but GFR <60 ml/min/1.73 m^2 for <90 days[b]
Non-recovery	Persistent RRT – RIFLE-L or -E	Persistent RRT – RIFLE-L or -E	RIFLE-F, -L or -E at hospital discharge, death or RRT	GFR <60 ml/min/1.73 m^2 for ≥90 days or persistent RRT

[a] In the ATN trial, patients with a 6-hour creatinine clearance >20 ml/min were trialed off RRT, whereas patients with a creatinine clearance <12 ml/min had RRT continued [25].

[b] The concept of AKD was introduced in the guideline as a way of classifying patients who did not recover after AKI but prior to 90 days when the CKD definitions apply.

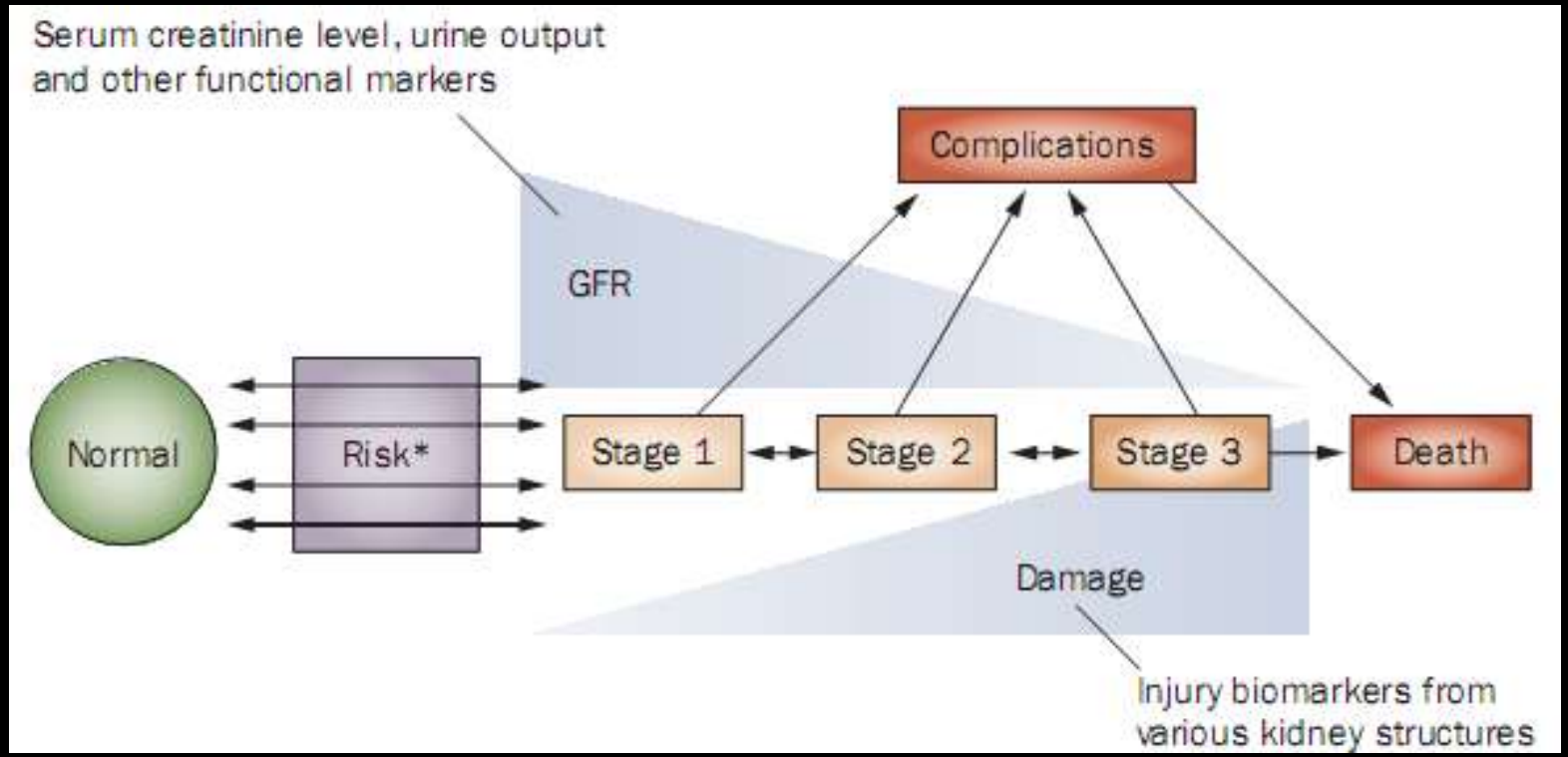
Action Plan



KDIGO 2012 KI supplements

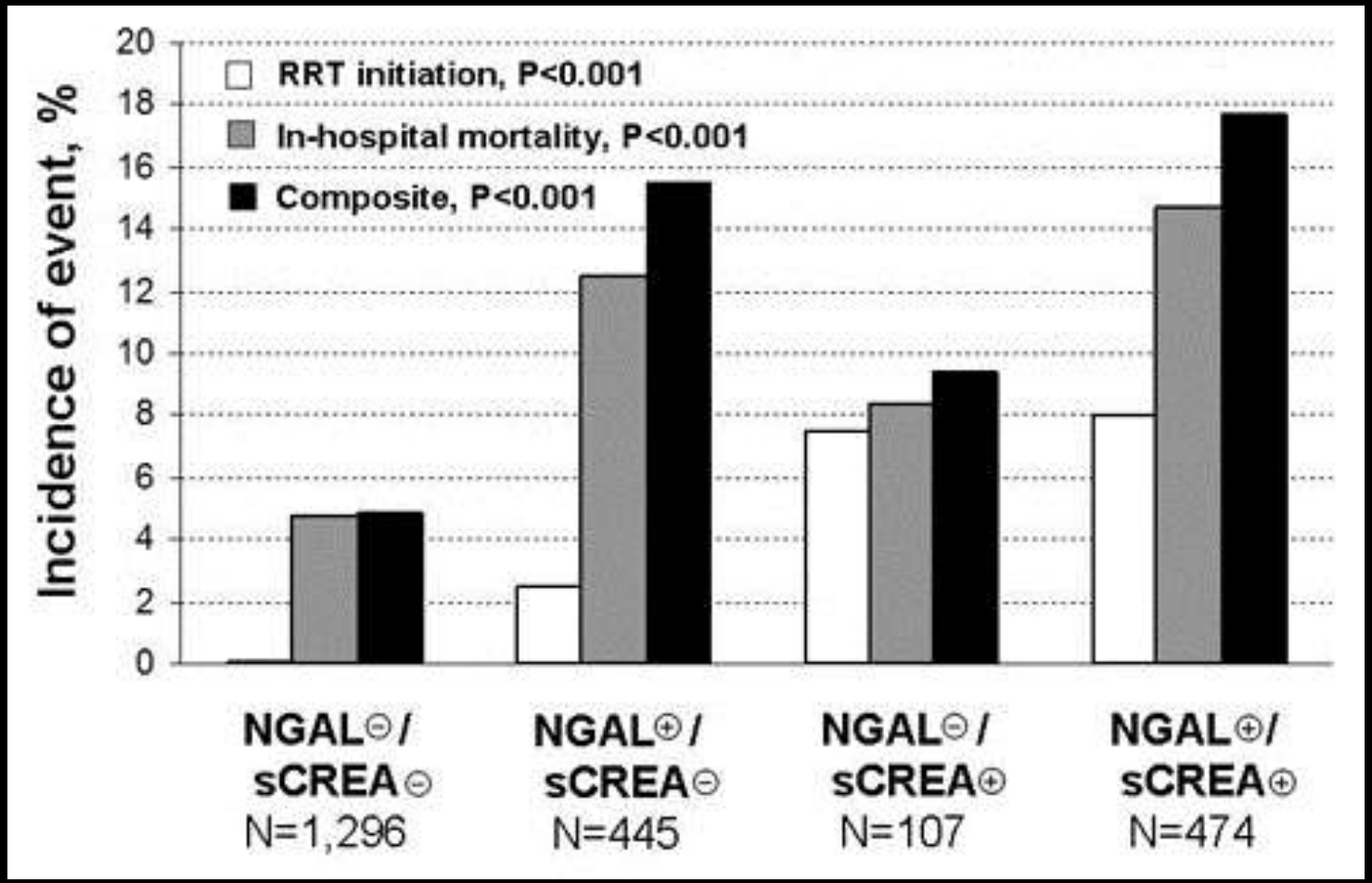
Acute kidney injury: what's the prognosis?

Raghavan Murugan and John A. Kellum



Subclinical AKI

Haase et al JACC 2011



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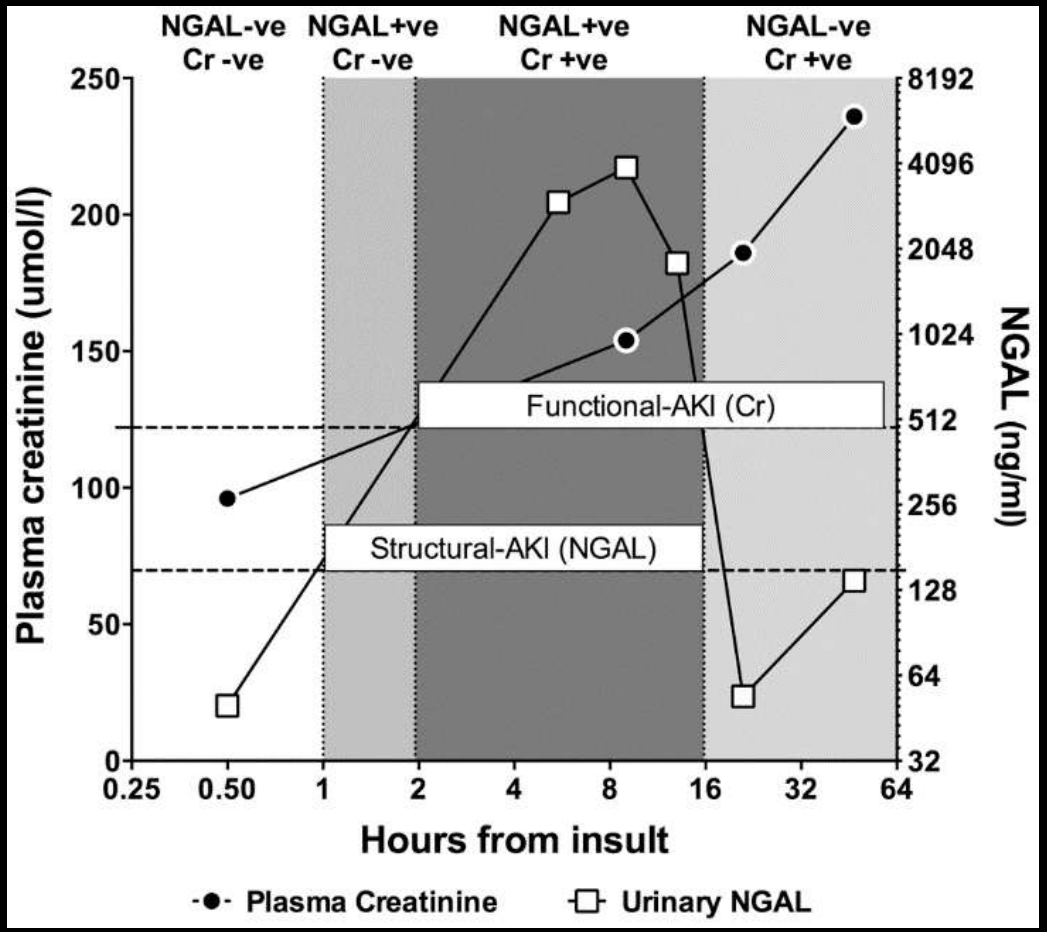
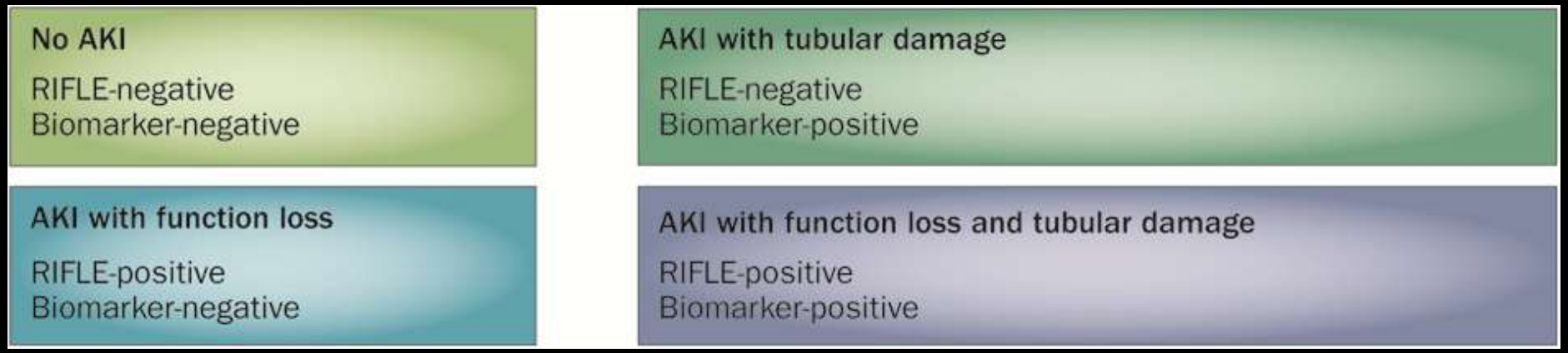


Subclinical AKI

an emerging syndrome with important consequences

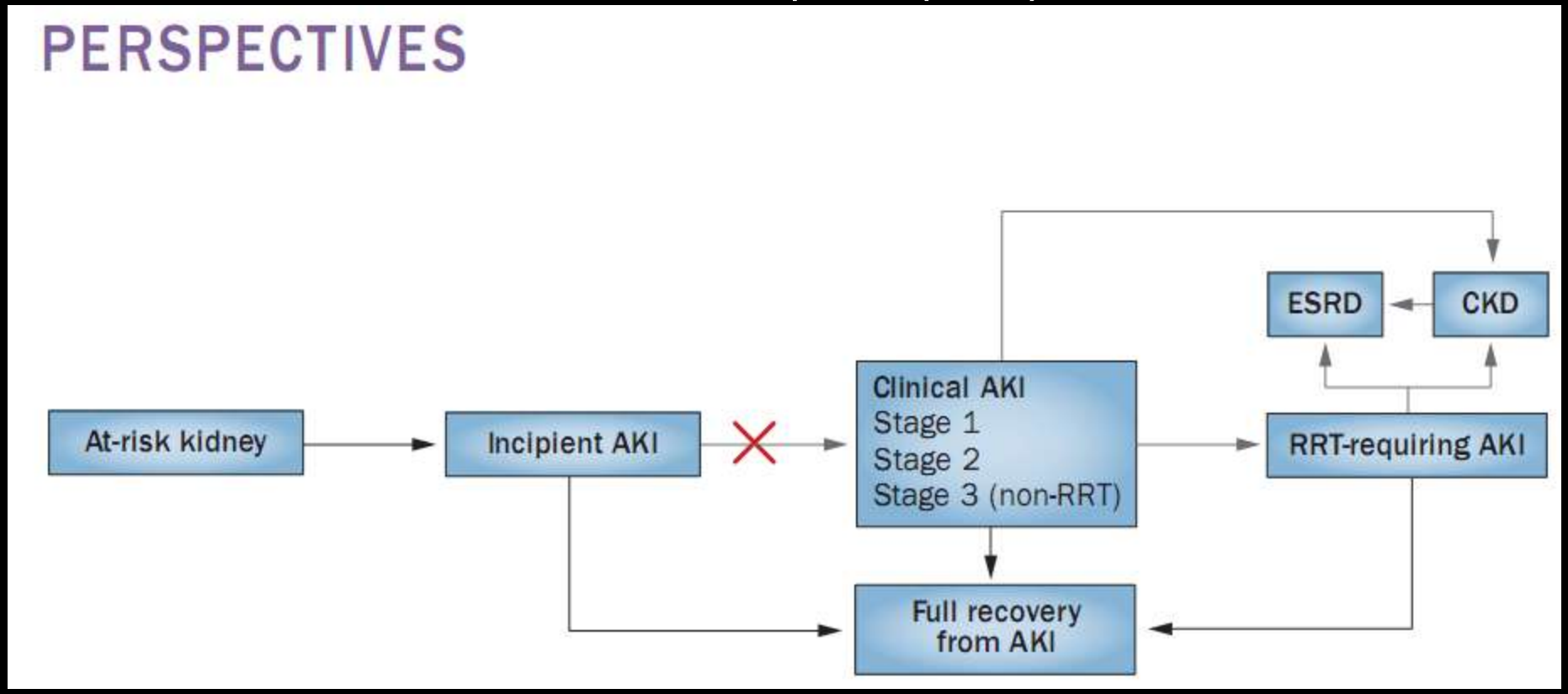
Haase *et al*.

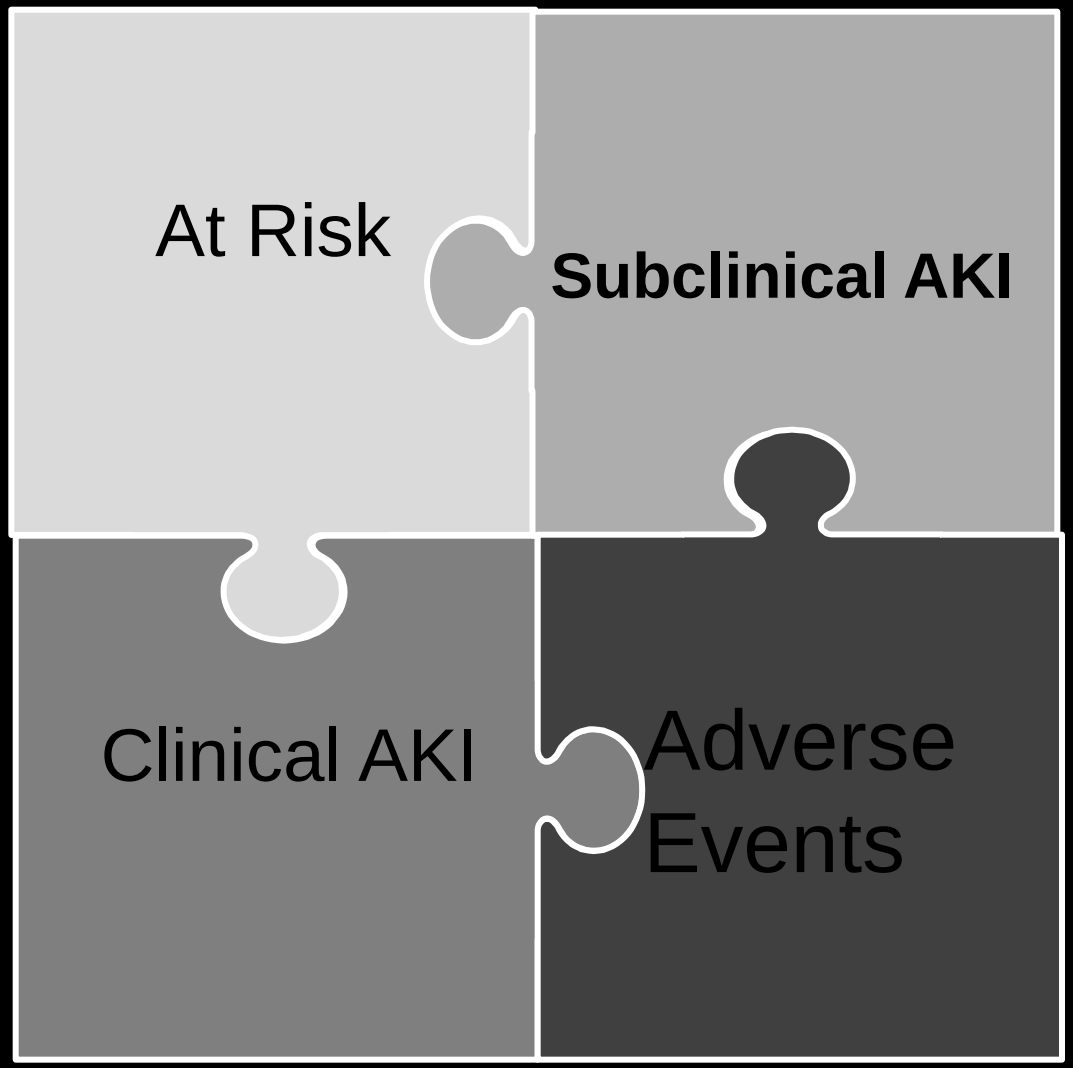
Nat. Rev. Nephrol (2012)



Subclinical AKI

Mark Perazella & Steven Coca
Nat. Rev. Nephrol. (2013)




At Risk
Subclinical AKI
Clinical AKI
Adverse Events

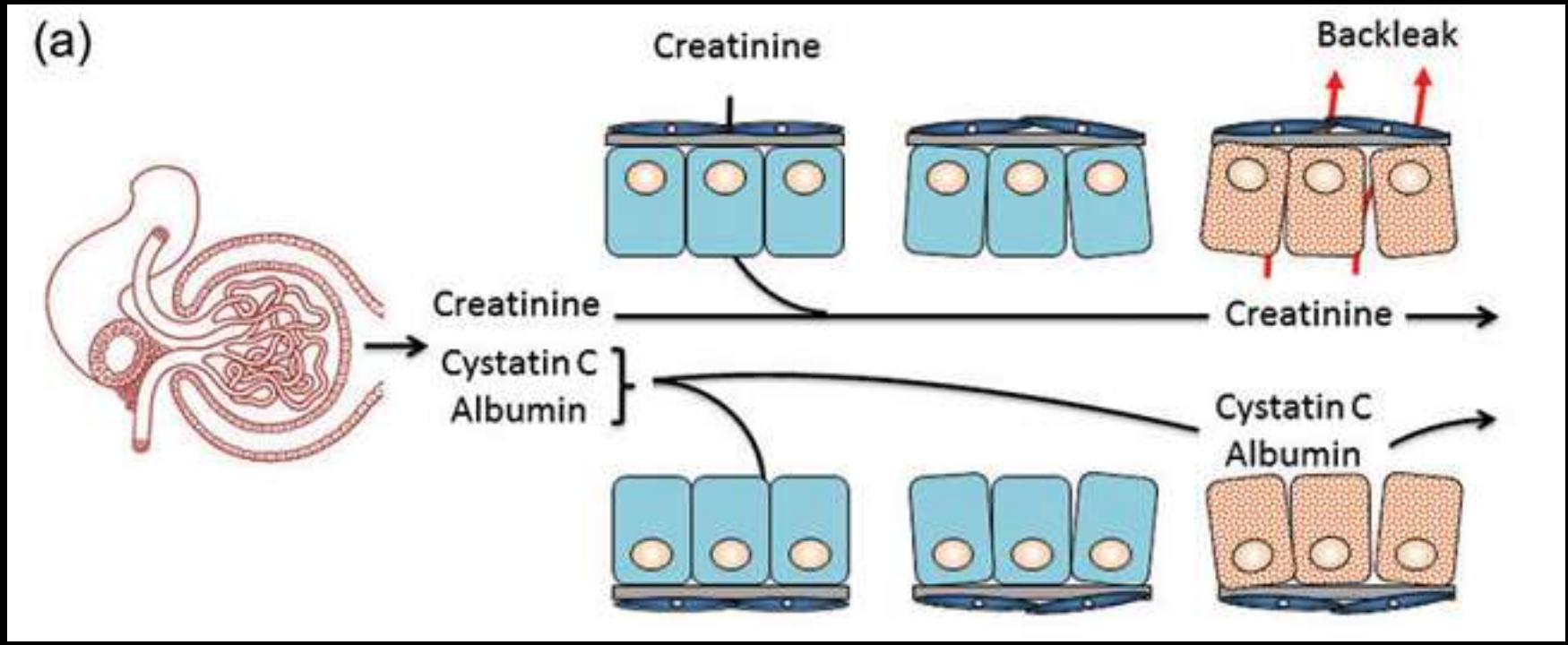
Kidney attack versus heart attack:
evolution of classification and diagnostic criteria

- Claudio Ronco, McCullough, Chawla
- ✓ lancet.com Vol 382 September 14, 2013

Heart	Kidney
ST-segment elevation myocardial infarction	Creatinine-increased AKI • Elevated AKI biomarkers • Change in serum creatinine or urine output
Non-ST-segment elevation myocardial infarction	Non-creatinine-increased AKI • Elevated AKI biomarkers
Unstable angina	Renal angina

Functional Biomarkers:

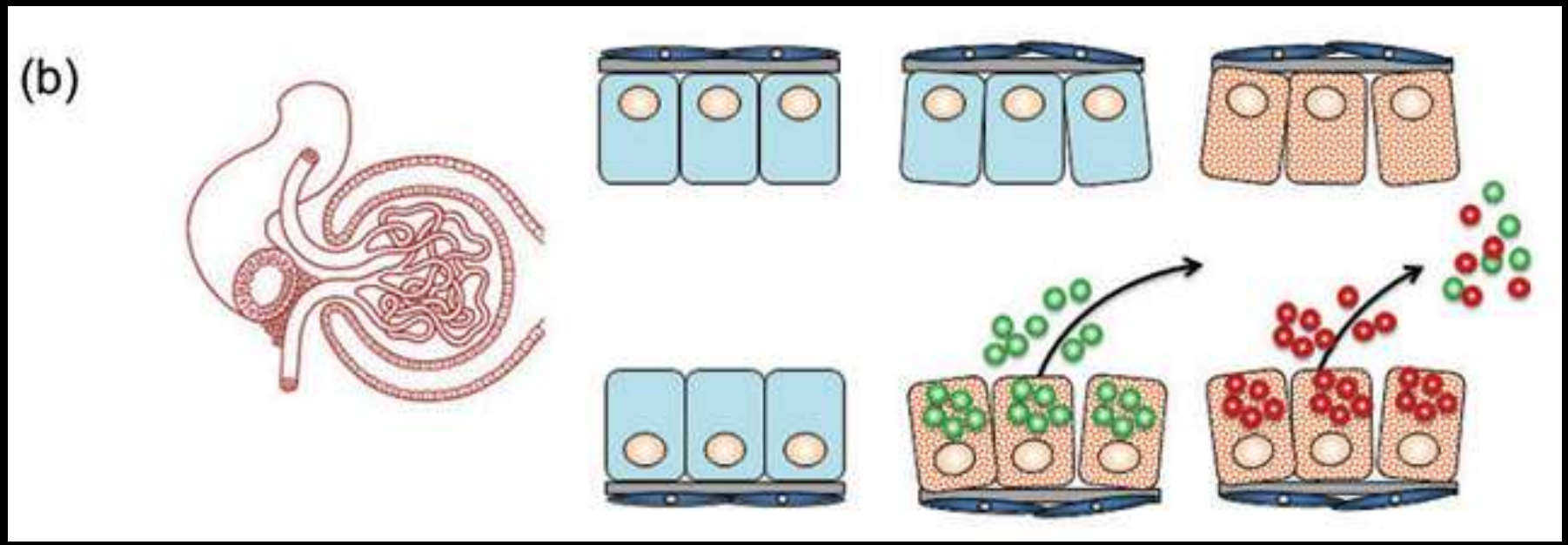
Okusa et al NDT 2014

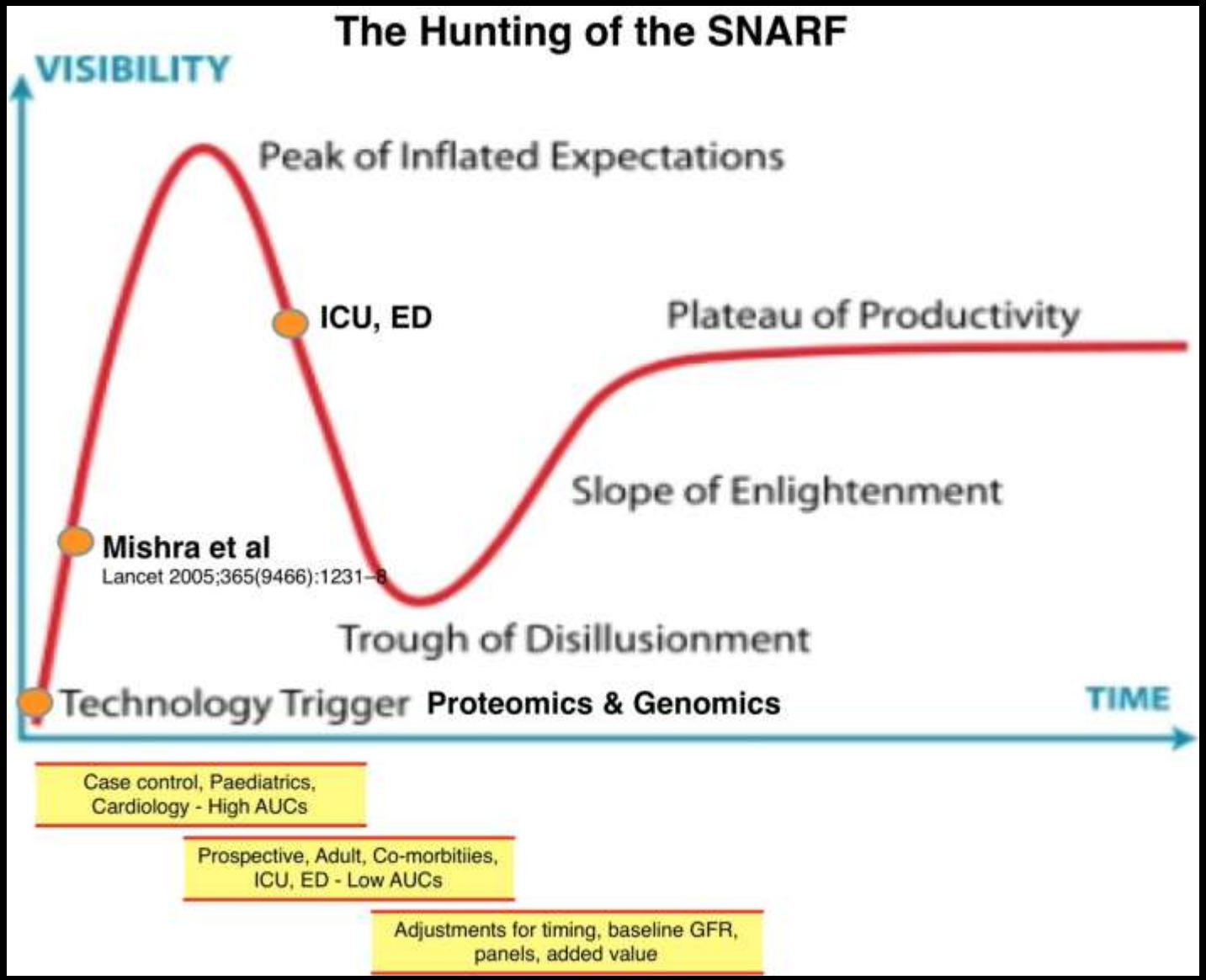


Damage Biomarkers

“Troponin of Kidney”

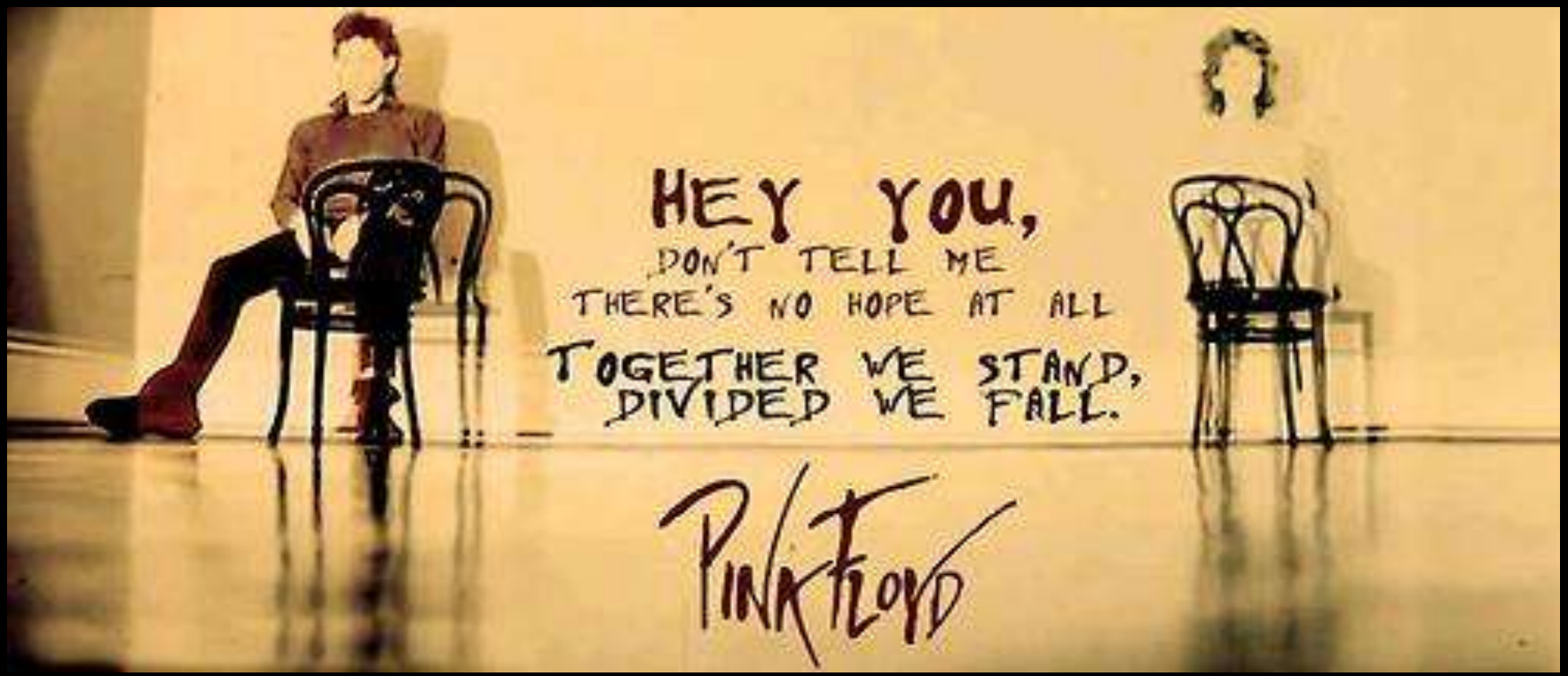
Okusa et al NDT 2014





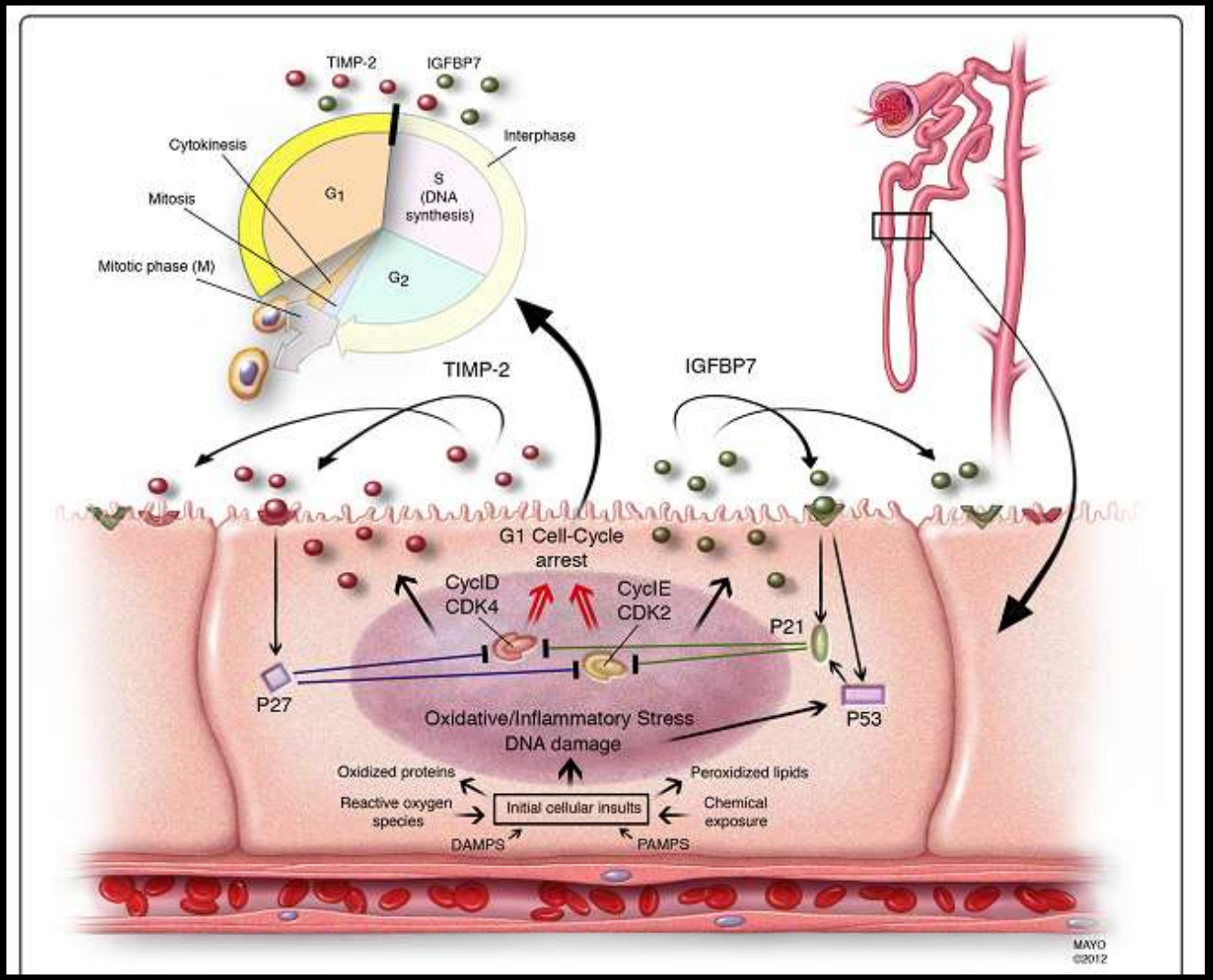
John Pickering
KI 2013

A Panel of Biomarkers…?



Discovery and Validation of Cell Cycle Arrest Biomarkers In Human AKI.

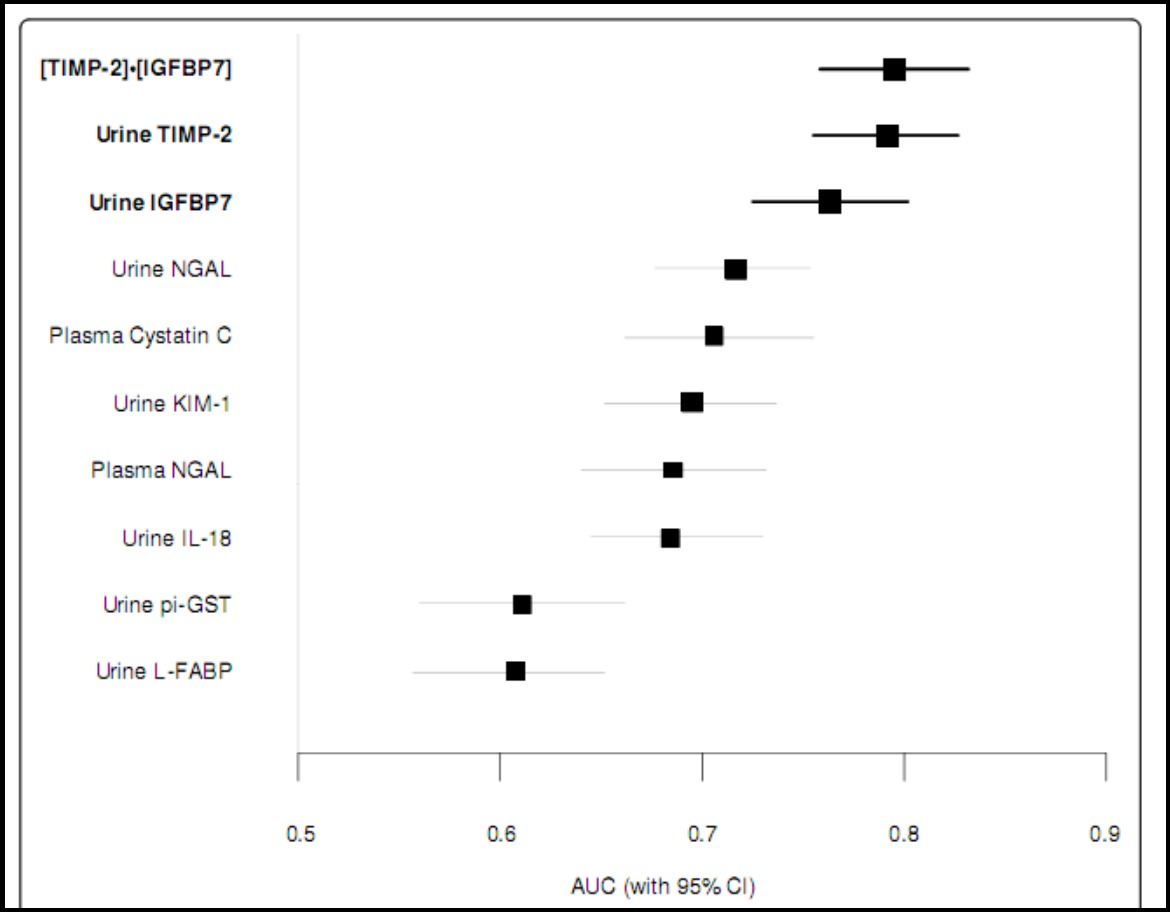
Kashani et al. Critical Care 2013



NephroCheck

Discovery and Validation of Cell Cycle Arrest Biomarkers In AKI (SAPPHIRE Study)

Kashani et al. (SAPPHIRE Study) Critical Care 2013



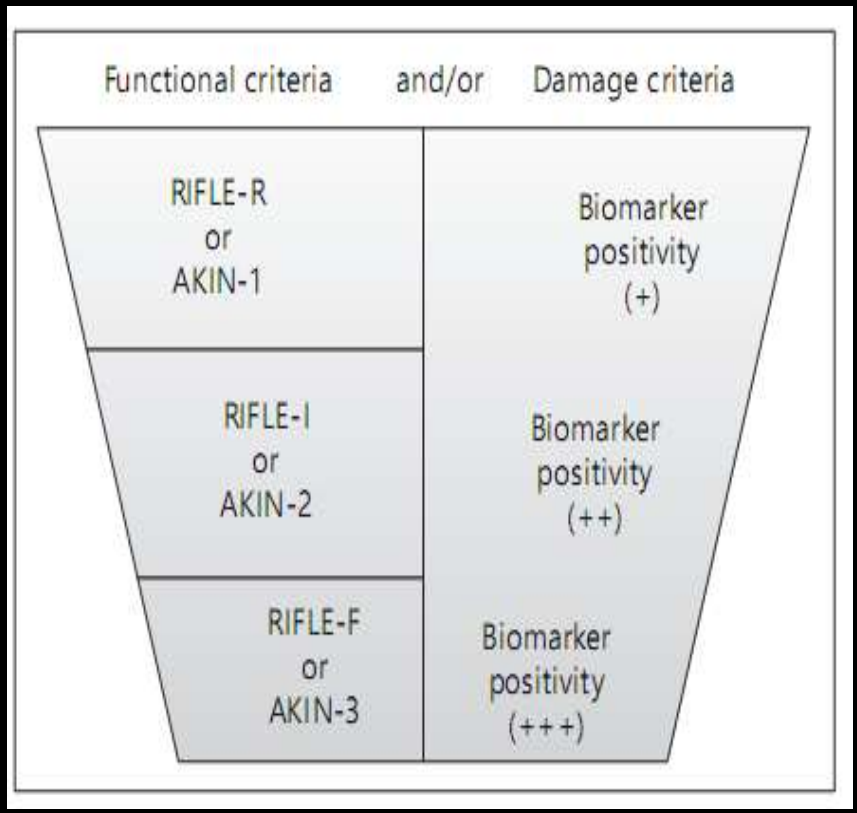
Defining AKI

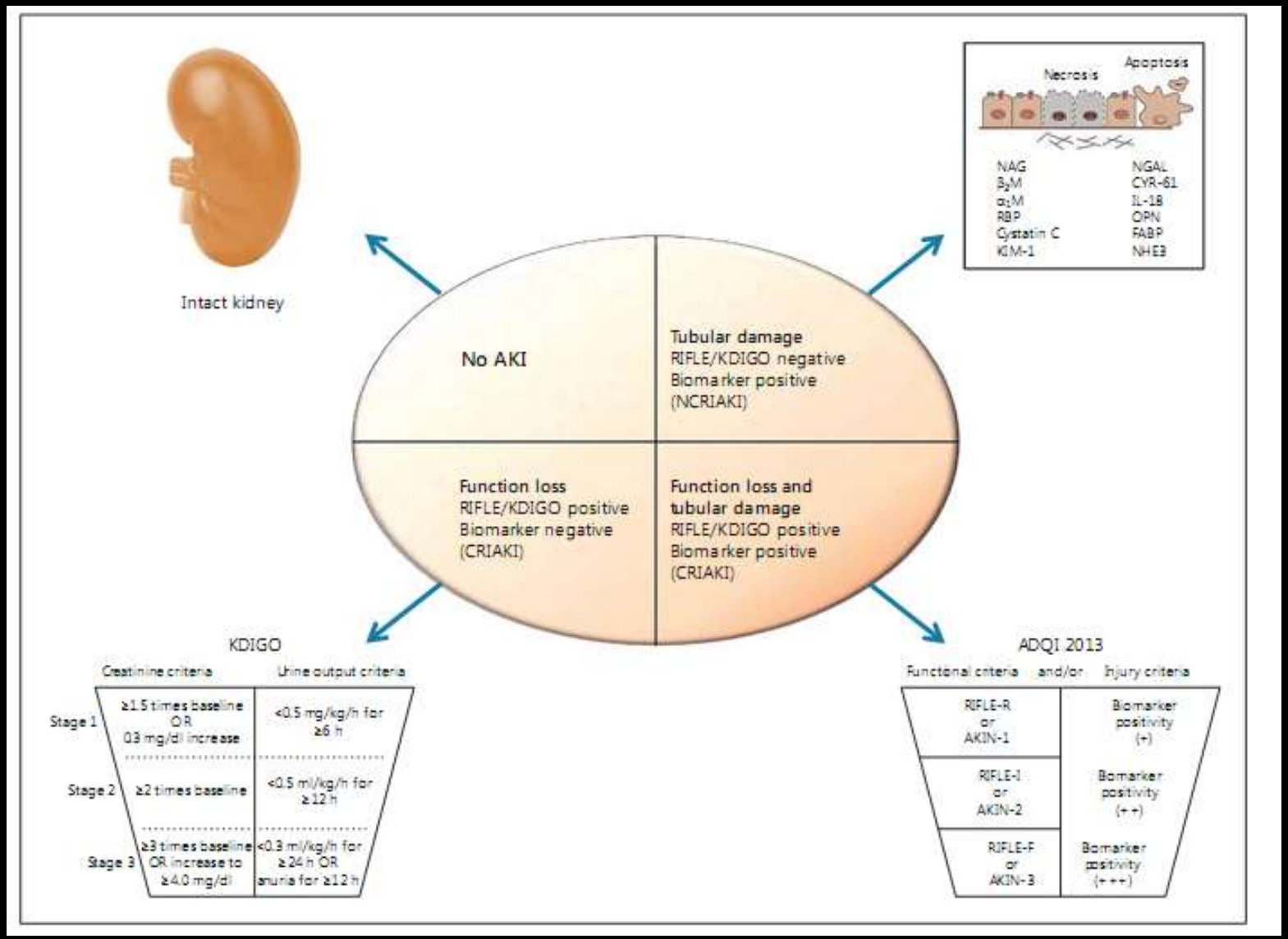
McCullough et al Nephrol. Clin Pract, 2013

OMICS Group:

"? AKI can be defined by abnormal levels of kidney injury biomarkers even in the absence of UO or SCr criteria?"

ADQI 2013: Novel Paradigm

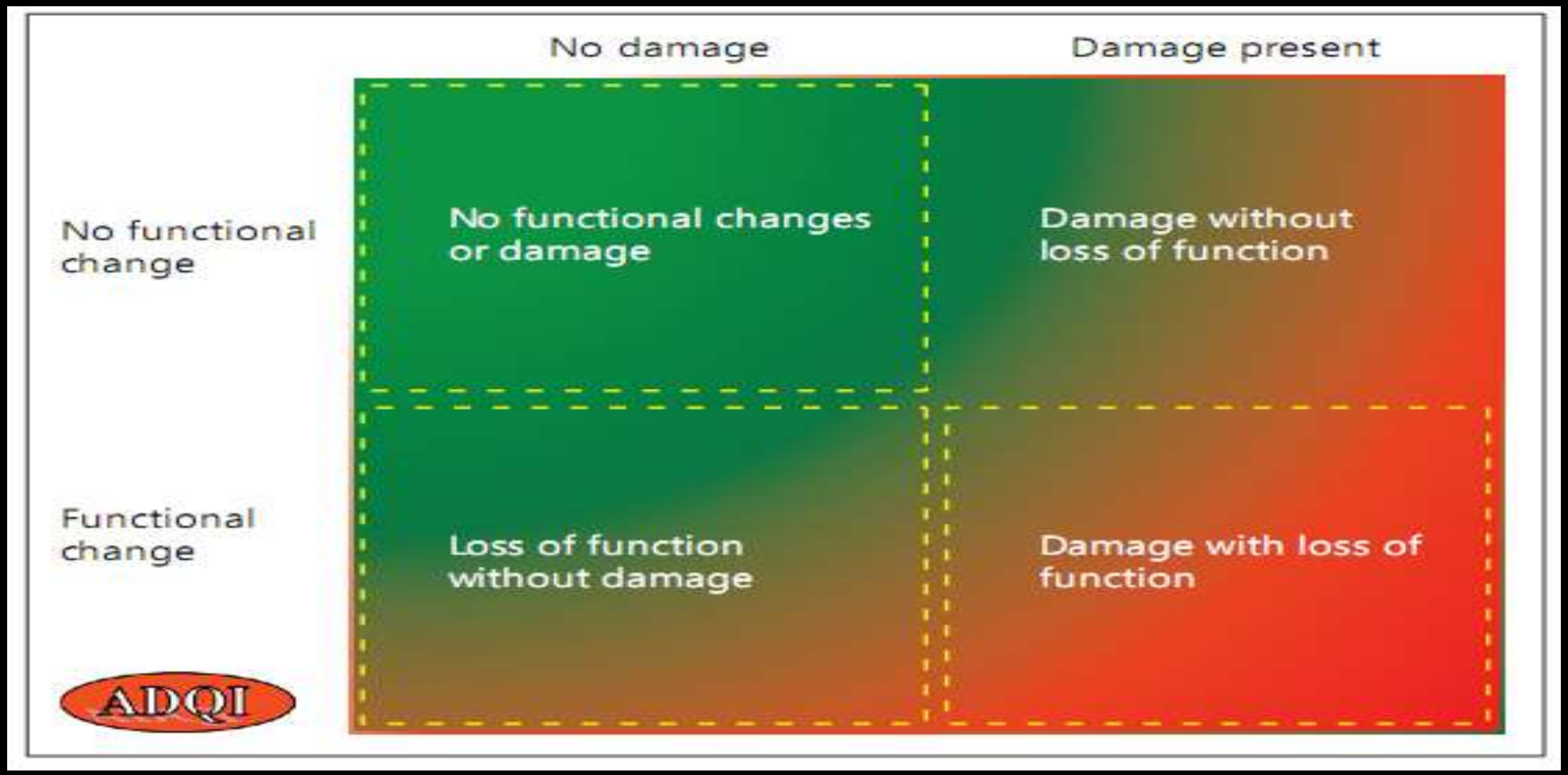


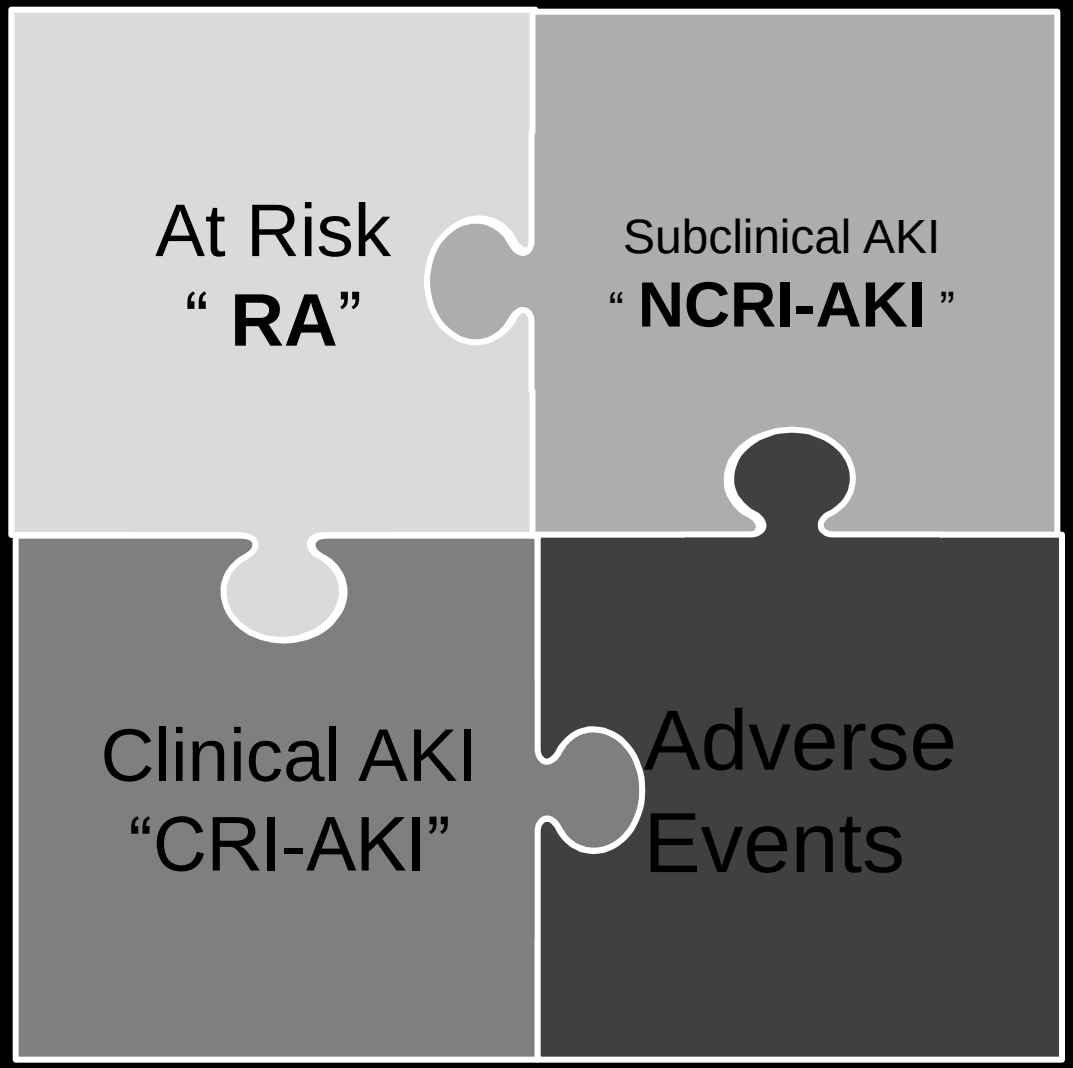

Intact kidney
Necrosis
Apoptosis
NAG
β_2M
α_1M
RBP
Cystatin C
KIM-1
NGAL
CYR-61
IL-18
OPN
FABP
NHE3
No AKI
Tubular damage
RIFLE/KDIGO negative
Biomarker positive
(NCRIAKI)
Function loss
RIFLE/KDIGO positive
Biomarker negative
(CRIAKI)
Function loss and
tubular damage
RIFLE/KDIGO positive
Biomarker positive
(CRIAKI)
KDIGO
Creatinine criteria
Urine output criteria
Stage 1
≥1.5 times baseline
OR
0.3 mg/dl increase
<0.5 mg/kg/h for
≥6 h
Stage 2
≥2 times baseline
<0.5 ml/kg/h for
≥12 h
Stage 3
≥3 times baseline
OR increase to
≥4.0 mg/dl
<0.3 ml/kg/h for
≥24 h OR
anuria for ≥12 h
ADQI 2013
Functional criteria
and/or
Injury criteria
RIFLE-R
or
AKIN-1
Biomarker
positivity
(+)
RIFLE-I
or
AKIN-2
Biomarker
positivity
(++)
RIFLE-F
or
AKIN-3
Biomarker
positivity
(+++)

ADQI 2013

Diagnosis of AKI

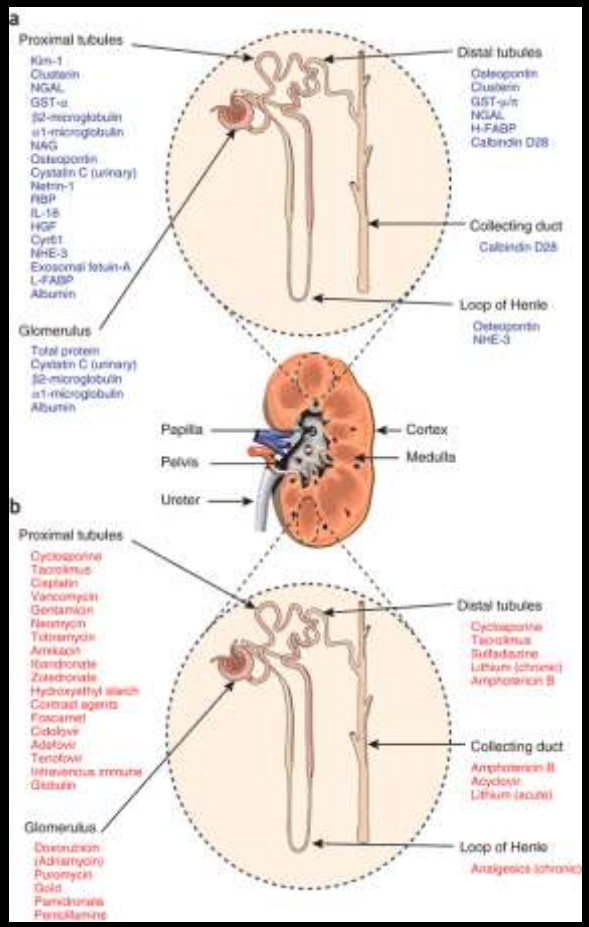
McCullough et al
Nephrol. Basel, Karger, 2013




At Risk
“ RA”
Subclinical AKI
“ NCRI-AKI ”
Clinical AKI
“CRI-AKI”
Adverse
Events

Biomarkers for detecting AKI

Bonventre et al nature biotechnology 2010



COMMENTARY

The concept of risk and the value of novel markers of acute kidney injury

Ronco and Ricci Critical Care 2013

Abstract

Kashani and colleagues studied two novel markers, insulin-like growth factor-binding protein 7 and tissue inhibitor of metalloproteinases-2, in the urine of patients at high risk of acute kidney injury (AKI). They validated these markers in a separate large multicenter study and compared them with known markers of AKI such as neutrophil gelatinase-associated lipocalin and kidney injury molecule-1. Insulin-like growth factor-binding protein 7 and tissue inhibitor of metalloproteinases-2 performed better than other known markers and their combination provided additional information. These markers could be useful in clinical practice to uncover silent episodes of AKI or to make an early identification of patients at risk. Ultimately they could help to detect and possibly prevent episodes of acute injury to the kidney, sometimes referred to as kidney attack.

Kidney attack versus heart attack:
evolution of classification and diagnostic criteria

- Claudio Ronco, McCullough, Chawla
- ✓ lancet.com Vol 382 September 14, 2013

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ST-segment elevation myocardial infarction	Creatinine-increased AKI • Elevated AKI biomarkers • Change in serum creatinine or urine output
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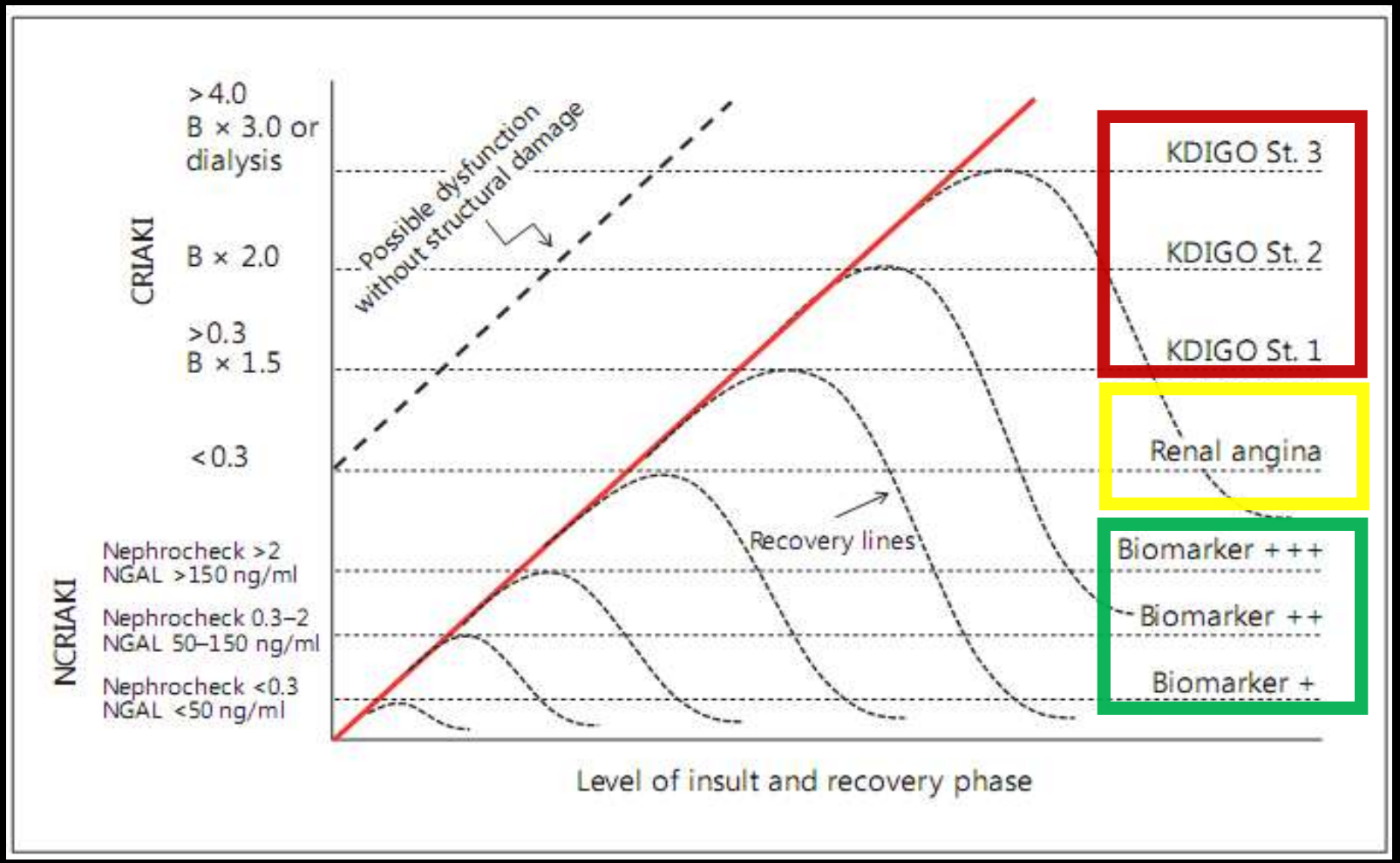
Unstable angina	Renal angina

Claudio Ronco
Blood Purif 2013

Kidney Attack



Molecular Biomarkers & Diagnosis

Ronco et al., J Mol Biomark Diagn 2014, 5:2
http://10.4172/2155-9929.1000164

Letter to the Editor Open Access

Heart Attack and Kidney Attack: Evolution of Lay and Clinical Terms for Spontaneous, Acute Organ Injury Syndromes

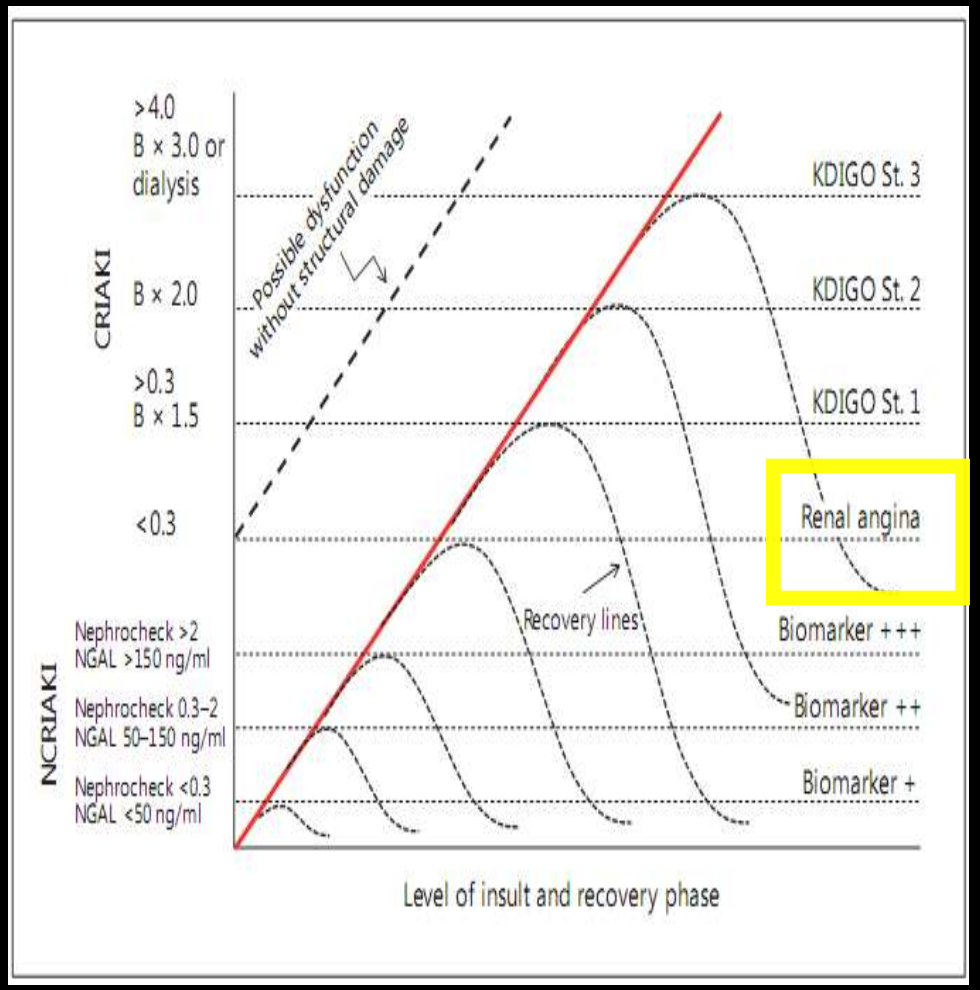
Claudio Ronco[1], Peter A. McCullough[2], Pupalan Iyngkaran[3]* and Lakhmir S Chawla[4]

HEART ATTACK*							KIDNEY ATTACK						
	Sym	Bio	EKGST	Th	EF	MI		Sym	UO	SCr	Bio	RF	RI
STEMI	++	↑	↑	+++	↓↓	++	Clinical AKI with Kidney Dysfunction						
							➢ AKI KDIGO Stage 1	-	↓	↑	↑	↓	+
							➢ AKI KDIGO Stage 2	-	↓↓	↑↑	↑↑	↓	++
							➢ AKI KDIGO Stage 3	-	↓↓↓	↑↑↑	↑↑	↓	++
NSTEMI	++	↑	↓	++	N/↓	±	Subclinical AKI with damage biomarker positive but dysfunction biomarker negative						
							➢ Damage Biomarker Trend	-	N	±	↗	±	±
							➢ Damage Biomarker Rise	-	N/↓	±	↑	±	+
UNSTABLE ANGINA	+	-	±/↓	+	N/↓	-	Renal Angina Recognition of renal stressors (e.g. hypotension)	+	↓	N/↑	N	↓	-

Kidney Attack

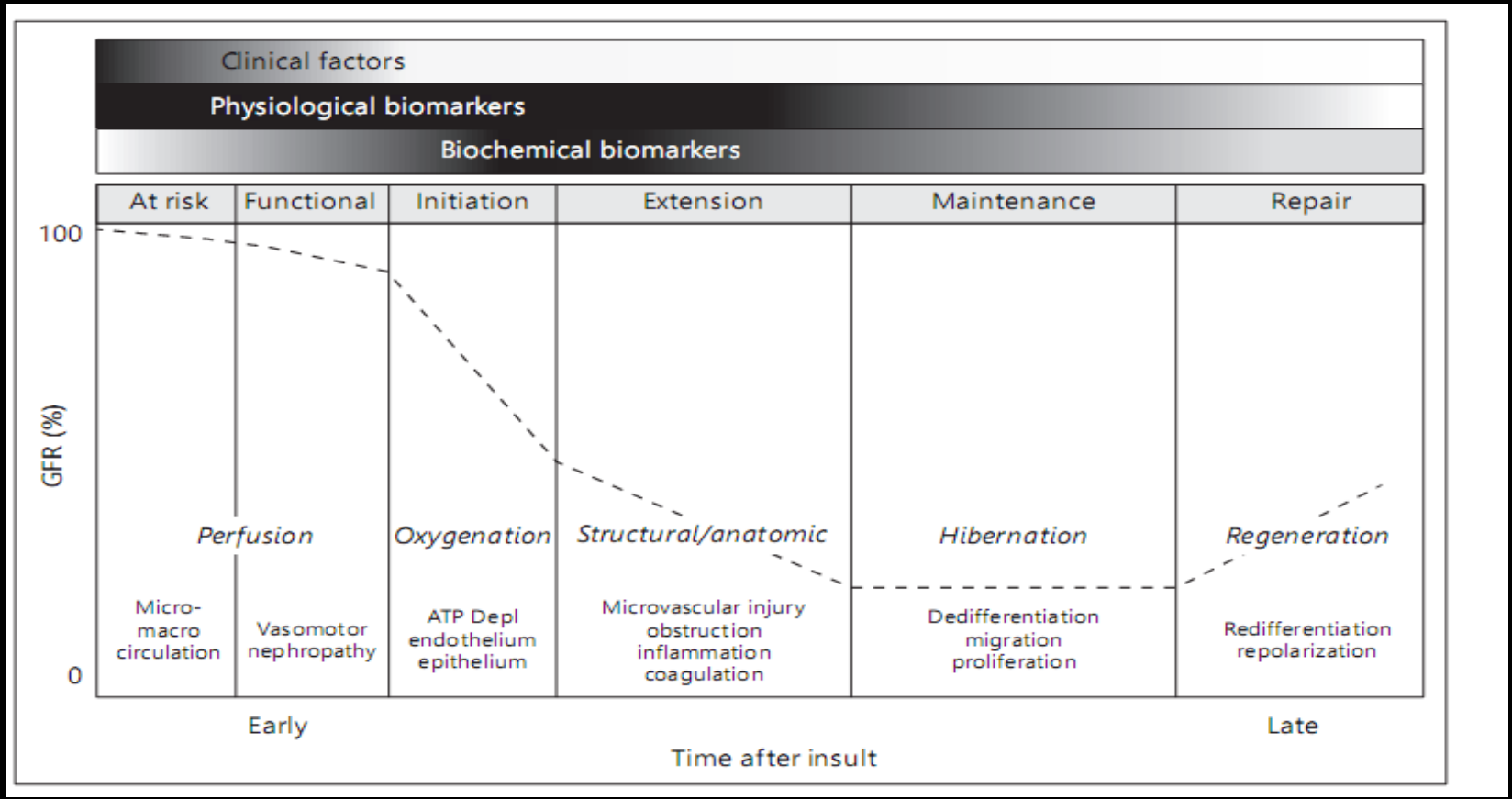
- Lay Term
- Intermediate Syndrome.
- Transition Stage.
- If AKI= ACS
- ✓ Renal Angina = UA

Claudio Ronco
Blood Purif 2013



Renal Functional Reserve(RFR)

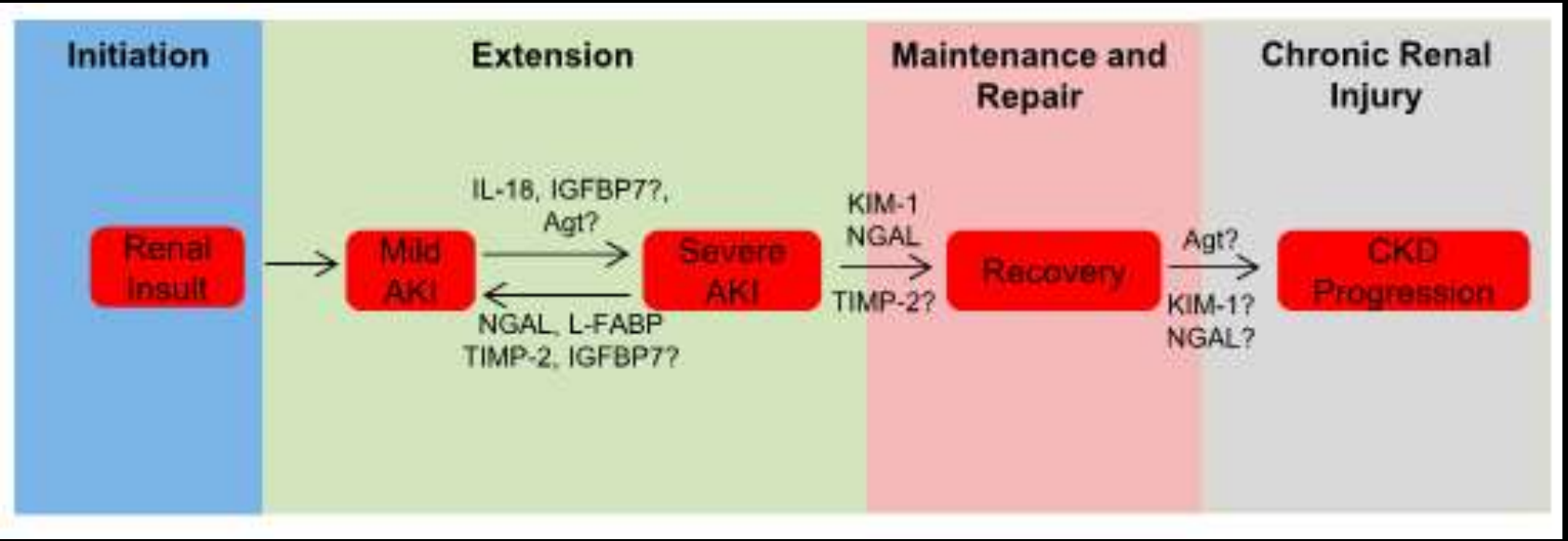
ADQI 2013:Physiological Biomarkers Okusa et al Nephrol. Clin Pract, 2013



Biomarkers of AKI:

Mechanistic Insights & Therapeutic implications

Alge and Arthur CJASN 2015



Clinical Trial Endpoints in AKI

Frederic Billings Andrew Shaw

Nephron Clin Pract 2014

Endpoint	Ease of measure-ment	Early expression	Mechanism insight	Long-term morbidity association	Low cost of measurement	Clinician comfort in assessment
RIFLE, AKIN, KDIGO urine output AKI criteria	***	***	*	*	*****	***
RIFLE, AKIN, KDIGO serum creatinine AKI criteria	****	**	*	**	****	***
Renal parenchymal damage biomarkers	*	*****	****	*	*	**
Renal function (clearance) biomarkers	*	****	*	*	*	**
Hemodialysis	*****	**	*	***	NA	****
New-onset CKD (stage 3 or higher)	***	*	*	****	****	****
Persistent renal function decline (>25% eGFR reduction)	***	*	*	****	****	****
CKD progression (from stage 3 or 4 to stage 4 or 5)	***	*	*	****	****	****
Death	*****	*	*	*****	*****	*****
MAKE30	***	*	*	***	****	***
MAKE60	***	*	*	****	****	***
MAKE90	***	*	*	*****	****	***

ADQI 2013:Physiological Biomarkers

Okusa et al Nephrol. Clin Pract, 2013

Table 1. Physiological biomarkers for assessment of kidney function in AKI

Glomerular filtration rate/urine flow monitoring
- Urine indices
- Real-time GFR measurement
- Serial serum creatinine measurement (with correction for fluid balance using bioelectrical impedance analysis)
- Continuous urine flow

Renal perfusion
- Doppler ultrasound (visualization of macrocirculation)
- Contrast-enhanced ultrasound (visualization of microcirculation)

Renal oxygenation
- Bladder tissue pO_2
- Bladder urine pO_2 (measure of renal medullary oxygenation)
- Near infrared spectroscopy (measure of renal O_2 bioavailability)
- BOLD MRI (measure of renal O_2 bioavailability)
- PET (measure of renal metabolism)

Other complimentary markers
- Kidney ultrasound
- Renal venous O_2 saturation (measure of renal oxygen consumption)
- Urinalysis (renal indices, urine sediment, flow cytometry)
- Endothelial markers (e.g. endothelial microparticles, glycocalyx degradation)
- Inflammatory markers (e.g. cytokines, immune cells)
- Oxidative stress markers

Furosemide Stress Test (FST):

Validation for predicting severity of AKI

Chawla et al. Critical Care 2013

Abstract

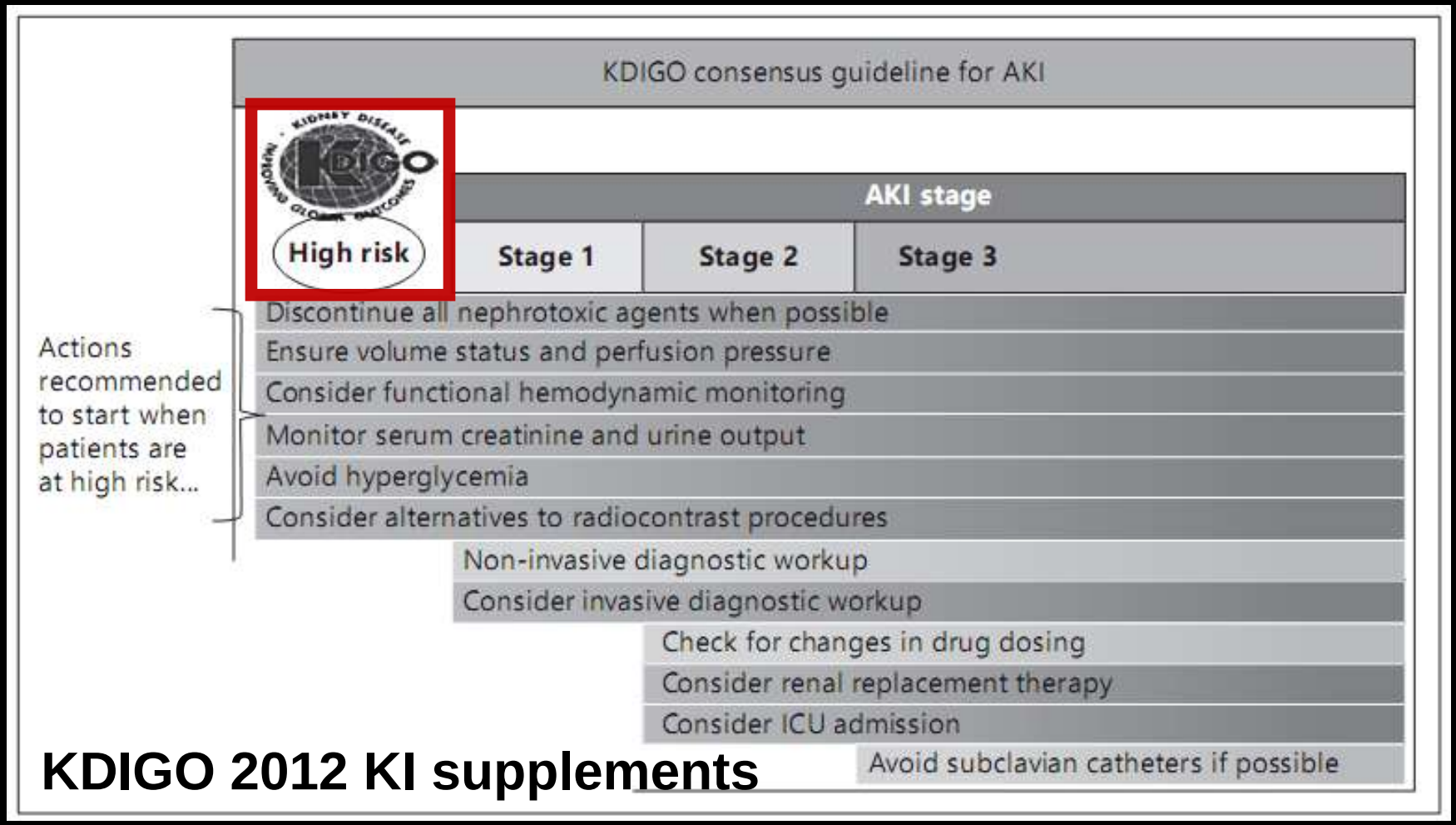
Introduction: In the setting of early acute kidney injury (AKI), no test has been shown to definitively predict the progression to more severe stages.

Methods: We investigated the ability of a furosemide stress test (FST) (one-time dose of 1.0 or 1.5 mg/kg depending on prior furosemide-exposure) to predict the development of AKIN Stage-III in 2 cohorts of critically ill subjects with early AKI. Cohort 1 was a retrospective cohort who received a FST in the setting of AKI in critically ill patients as part of Southern AKI Network. Cohort 2 was a prospective multicenter group of critically ill patients who received their FST in the setting of early AKI.

Results: We studied 77 subjects; 23 from cohort 1 and 54 from cohort 2; 25 (32.4%) met the primary endpoint of progression to AKIN-III. Subjects with progressive AKI had significantly lower urine output following FST in each of the first 6 hours ($p<0.001$). The area under the receiver operator characteristic curves for the total urine output over the first 2 hours following FST to predict progression to AKIN-III was 0.87 ($p = 0.001$). The ideal-cutoff for predicting AKI progression during the first 2 hours following FST was a urine volume of less than 200mls(100ml/hr) with a sensitivity of 87.1% and specificity 84.1%.

Conclusions: The FST in subjects with early AKI serves as a novel assessment of tubular function with robust predictive capacity to identify those patients with severe and progressive AKI. Future studies to validate these findings are warranted.

Action Plan



KDIGO 2012 KI supplements

Redefining “Physiology”

- ✓ATN to AKI.
- ✓Static to dynamic.
- ✓Pre-renal to volume responsive.
- ✓Liberal to Restrictive.
- ✓Normal to Balanced.

From AKI to Kidney Attack


FINISH

The End


Thank You!